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ANNUAL REPORT OF PROGRAM ACTIVITIES

DIVISION OF RESEARCH RESOURCES

FISCAL YEAR 1971

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

DIVISION OF RESEARCH RESOURCES

Fiscal Year 1971

ANNUAL REPORT

FISCAL YEAR 1971
(July 1, 1970 - June 30, 1971)

DIVISION OF RESEARCH RESOURCES

U.S. National Institutes of Health, Division of Research Resources

Bethesda, Md. 20014

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REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

Report of the Division Director

In both the Fiscal Years 1969 and 1970 Annual Reports, I raised a pessimistic outlook concerning the future viability of the Division, not because of lack of "....confidence in the Division's program concepts and the capability of its staff....", but rather, with the severe budgetary restraints facing the Division I questioned whether we would be able to effectively respond to the needs of the research community.

Two significant factors which occurred during the Fiscal Year 1971 have however induced me to temper somewhat my previous attitude and approach the new fiscal year with renewed enthusiasm. The first of these events was that on October 6, 1970, the Division, as part of the reorganization of the Bureau of Health Professions Eduation and Manpower Training, became an independent Division within the research components of the National Institutes of Health. This organizational change has given greater visibility both within and without the NIH to the role of the DRR in the execution of the Institutional research support program policies of the NIH.

The second event of consequence was that the Fiscal Year 1971 budget provided increases for the General Clinical Research Centers Program, the Animal Resources Program, and for the Primate Centers Program. The increase in the budget for the latter program was especially significant since it precluded the closure of at least one of the seven Primate Centers.

Of continual concern to us, however, is the fact that despite the documented evidence of the worth of the General Research Support Program, the budget for this program was once again reduced and still further reductions appear in the President's Budget Request for Fiscal Year 1972.

Within the Division, several organizational changes were made. On November 3, 1970, the name of the Special Research Resources Branch was changed to the Biotechnology Resources Branch to give greater identity to the nature of the programs supported. On March 23, 1971, the Program Analysis Branch was established, replacing the old Office of Program Analysis. This latter organizational change reflected the increased emphasis being placed on program analysis activities in the Division. Authority for the National Advisory Research Resources Council to review the General Research Support Grant Program was obtained on March 14, 1971. This authority had previously been vested with the National Advisory Health Council. All of the Division's programs are now reviewed by the National Advisory Research Resources Council.

Several notable staffing changes occurred during the year in the Office of the Director. Dr. James F. O'Donnell was appointed Assistant Director; Mr. David L. Chicchirichi, Executive Officer; and Mr. Richard L. Shafer, Administrative Officer. Dr. Charles W. McPherson was appointed Chief, Animal Resources Branch. Dr. Carl R. Brewer, formerly Chief, General Research Support (GRS) Branch, was named Special Assistant for Institutional Relations. Dr. Robert J. Gibbs succeeded Dr. Brewer as Chief, GRS Branch.

A significant program development this year was the initiation of the resource-related research grant as a funding mechanism within the Biotechnology Resources

Branch. Through this mechanism, the Branch can support sophisticated biomedical research at a resource which is being currently supported by other than NIH funds. The first of these awards was made this year.

Thus, during the past year DRR has regained much of the momentum lost during reorganization with the Bureau of Health Professions and Manpower Training; made key staffing changes; weathered several fiscal crises; and is moving forward again confident, albeit cautious.

DRR BRANCH REPORTS

Fiscal Year 1971
ANNUAL REPORT

Biotechnology Resources Branch
Division of Research Resources

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FISCAL YEAR 1971
ANNUAL REPORT
BIOTECHNOLOGY RESOURCES BRANCH
DIVISION OF RESEARCH RESOURCES

During Fiscal Year 1971 the Biotechnology Resources Branch (BRB) continued to make available to grantees and contractors of the various NIH categorical programs the kinds of tools without which their research efforts would be seriously hampered, if not precluded entirely. Emphasizing digital computation, mass spectrometry, nuclear magnetic resonance spectroscopy, and electron microscopy, the BRB and its clientele have been increasingly successful in establishing a mutually enriching interplay between biology and medicine on the one hand and the physical sciences, mathematics, and engineering on the other. This past year demonstrated more than ever before that regional centers of scientific and technical excellence such as the Biotechnology Resources can be a powerful administrative form for encouraging multidisciplinary inquiry and for bringing the results of technological innovation smoothly and quickly to the service of the biomedical community. This report highlights a few of the many BRB-sponsored activities whose accomplishments during the past year are eloquent testimony to the viability and importance of the research resource concept.

GENERAL PROGRAM INFORMATION

During FY 1971 the BRB provided support to 51 resources, 1 resource-related research project, and 2 contracts at an aggregate funding level of $9,757,000. As in previous years the bulk of the branch's expenditures ($8,312,523) supported computer resources, underscoring the fact that this technology takes more forms and has greater breadth of applicability to health research problems than any other. Nevertheless, this strong commitment to the support of digital computation has not prevented the BRB from continuing its emphasis on mass spectrometry and nuclear magnetic spectroscopy, or from increasing its impact in the area of high voltage electron microscopy. Overall, the staff and its advisors have achieved an effective balance between the exploration of new technologies, and the continued support of established research tools vital to NIH categorical programs.

SUPPORT OF CATEGORICAL PROGRAMS

One of the primary measures of accomplishment that can be applied to the Biotechnology Resources Program is the extent to which its sponsored activities markedly assist the various NIH categorical programs. With their cadres of highly skilled staff scientists, and their specialized and often unique facilities, Biotechnology Resources are frequently the scene of productive encounters between experts in a given technology and experts in a given medical discipline. These examples are but a few of the many such encounters during the past year:

Cardiovascular Research

At Washington University in St. Louis, Missouri, the digital computer is finding yet another new application as a tool for human clinical investigation. The Biotechnology Resource at this institution has for many years been one of the leading centers in the Nation developing techniques for the automatic monitoring of heart rhythms. The resource personnel have designed and put into routine operation in a coronary intensive care unit a network of small computers which continuously record and analyze the cardiac rhythm patterns of every patient in the unit. This computer network not only alerts the attending medical personnel to the occurrence of unusual heart rhythms (which often presage impending cardiac crisis), but also records the measurements in computer-based files to allow subsequent retrieval and detailed analysis. This computer system will soon be produced by a commercial organization and, thus, will be available to other centers throughout the Nation.

Even more exciting than its routine patient care applications is the computer system's uses in clinical research. Because it can make measurements reliably and precisely for long epochs, the computer system can provide scientists with sufficient data to put many of their estimates about the status of the heart's functioning on a statistical basis. This opportunity to perform more vigorous experimentation should be especially valuable in cases such as the clinical trials of drugs which affect heart rhythm. It seems inevitable that the ability to routinely obtain statistically valid measurements on human subjects will lead to better understanding of the consequences of these agents and, hence, both to improved efficacy and to increased experimentation to unravel the actual mechanisms by which the drugs act.

Cancer Research

Computer methods have also had an important impact on cancer research as is illustrated by the work at the Biotechnology Resource at the University of Pennsylvania. In this case the investigators have developed a computer program which automatically determines the growth rate characteristics of tumor cell populations, given data on the extent of the uptake of radioactively labelled material by the cells' DNA molecules during cell division. Once these growth rate characteristics are known, it is possible to predict how the tumor will behave under various conditions and/or to select drugs and dosage schedules to combat the tumor via chemotherapy. The analysis is based on a complete model of how cell populations divide and grow, and it represents a level of computation which can only be carried out by electronic means.

Human Reproductive Mechanisms Research

The Biotechnology Resource at the University of Pittsburgh has applied the techniques of gas chromatography and mass spectrometry to research projects involving the mechanisms of spontaneous abortum and the cause of male infertility. In both instances the research focuses upon the role of prostaglandins, small-molecule hormones which are of widespread occurrence in the human body and which are thought to have a crucial function in many reproductive processes. There are many known prostaglandins, and the ability to associate the presence or absence of specific ones with various physiological states could contribute much to understanding the normal and abnormal biochemistry of human reproduction.

The importance of gas chromatography and mass spectrometry to this research results from the investigators' need to identify the presence or absence of specific prostaglandins in small quantities of human tissue fluids (e.g., amniotic or semen). The resource at the University of Pittsburgh can perform these analyses routinely and thereby bring to bear on these problems a set of tools that is at the leading edge of the state-of-the-art. Not only will this line of research become increasingly more significant but, as interest throughout the Nation in the subject of synthetic prostaglandins and their possible role in contraception grows, gas chromatography and mass spectrometry will almost inevitably be relied upon to identify and characterize the structures of the substances under investigation.

Transplantation Immunology and Human Genetics Research

In many cases the expertise possessed by the staff of a Biotechnology Resource is far more important than even the specialized facilities that it makes available, and nowhere is this better illustrated than in the transplantation immunology research being performed at UCLA. This project represents a long-term collaboration between a major user of the resource and a senior resource staff member. The goals of the project are the elucidation of the full set of human tissue types and the development of means to identify them quickly and economically. If well understood, the ability to "type" human tissues similar to the way blood is "typed" would certainly allow for closer matches between donors and recipients in transplant interactions and markedly reduce the likelihood that the recipient's immunological system would eventually reject the foreign organ.

In addition to providing excellent computer services, the UCLA resource has made major substantive contributions which have proved indispensible to progress on this project. Most notable is the discovery and refinement of a new statistical method (Boolean factor analysis) which is specially tailored to deal with the type of analyses required in the search for tissue types via serological procedures--i.e., explaining the patterns of "reaction/no reaction" results from large series of cross matches between suspensions of white blood cells and various sera. With over two dozen tissue types already known and many others anticipated, it would be almost impossible to carry out these studies in the absence of these powerful statistical methods and the supporting computer installations. Moreover, as the genetic basis of these tissue types become better understood, the computer will take on additional functions in both the storage of information on many individuals and the testing of genetic models designed to explain the data.

TECHNOLOGICAL INNOVATIONS CONTRIBUTED BY BIOTECHNOLOGY RESOURCES

The major reason that Biotechnology Resources have been able to build a record of high quality service to and research collaboration with the grantees and contractors of almost every NIH categorical program is not difficult to identify: it can be given in a single phrase--core research. Since technologies such as digital computation, mass spectrometry, and the like are evolving as rapidly (and in some cases as unpredictably) as biomedical science, a resource would soon begin to fail its clientele badly if its staff were not able to have the center's capabilities at any point in time reasonably approximate the state-of-the-art. And, indeed, since the resource staff frequently select their own areas of investigation as a result of the demands which biomedical problems are placing upon their technology, the research resource can do much to insure that the tools are fitted to the need and not vice versa. In the following paragraphs a sampling of such core research efforts is presented.

Attainment of Atomic Resolution With Computer-Assisted Electron Microscopy

One of the most spectacular technological achievements produced anywhere in the Nation was recently accomplished by the Biotechnology Resource at the Jet Propulsion Laboratory of the California Institute of Technology. As part of its overall program in biomedical image processing, this resource has concentrated upon methods for enhancing the resolution of electron microscopes. In brief, the staff at the JPL resource combined a complex set of computer programs for image enhancement and "noise" elimination to improve the quality of the ordinary microscope image and then applied to the diffraction patterns a set of mathematical procedures essentially identical

to those used by X-ray crystallographers. The result was an image with resolution in the range of 1 Ångstrom--sufficient detail in at least some preliminary areas to discern individual atoms.

The JPL group is now actively working to make this computer-assisted microscopy technique available on a relatively routine basis so they and their collaborators can apply it to many molecules over and above the few organic crystalline materials (e.g., the dye indanthrene olive) which have been employed to date. These additional studies involve experiments with a high vacuum microscope and extensions of the computer's role to actual control of the instrument itself. The latter is especially important where large biomolecules are involved, because the increased speed of focusing and final-imaging the molecule under observation will lessen the likelihood that there will be structural alteration (or complete destruction) of the material by the electron beam before a micrograph can be made.

Structural Analysis of Large Biomolecules by Mass Spectrometry

At the Yale University Biotechnology Resource the elucidation of complex molecular structures is also the goal, but the methodological approach differs from that of the JPL resource. The Yale group has been experimenting with techniques for introducing large molecules (such as proteins) into mass spectrometers in a reproducible and efficient manner. The scarcity of methods for doing this has severely limited the utility of mass spectrometry in this area of biomedical science--the low volatility of these substances being the primary obstacle.

The Yale group has begun to overcome this obstacle by finding ways to produce sprays of droplets of various solvent systems, each droplet ideally containing a single large molecule. This spray is then introduced into the mass spectrometer, and the analysis carried out. While this technique is only in its preliminary stages, and many technical problems need be resolved before routine application is feasible, it seems clear that this will be a fruitful approach. This project demonstrates how the expertise and insight of a resource's staff with regard to a major problem besetting the biomedical community can find tangible expression in the form of a technique which can eventually be placed into direct application within the setting of its origin.

On-Line Acquisition and Analysis of High Data Rate Signals

One of the major problem areas in biomedical computation is the processing of high data rate signals from experimental animals and human subjects in real time. This problem is especially acute in the field of neurophysiology where many thousands of data-points must be handled each second in order to achieve the required degree of temporal resolution (e.g., to discern the initial, fast rising portion of a nerve cell's action potential). A given investigator's options for experimental inquiry in this field are severely limited by the measurement techniques he has available to him. A major step forward in the handling of high data rate signals via digital computer has recently been completed by the personnel of the Biotechnology Resource at the University of Alabama. This group has designed and built a computer network which can not only serve several high data users simultaneously but can also guarantee that once a user enters the system there will be no degradation in the service to his respective station. No other system offers this feature. The users of this resource now have available to them a unique facility for on-line computation, and their experiences over the next few years will not only shape the future development of the Alabama system but also influence the extent to which the system (or at least the concepts upon which it is based) finds application in other research settings.

NEW BIOTECHNOLOGY RESOURCES

During FY 1971 the BRB was able to add five new efforts to its list of sponsored activities--2 in digital computation, 1 in mass spectrometry, 1 in nuclear magnetic resonance, and 1 in electron microscopy. While these activities have in common extremely high scientific merit ratings, they differ markedly both in their objectives and in the nature of the opportunities they will offer to biomedical scientists in their geographic regions.

Digital Computation I: Pennsylvania State University Medical School

This resource actually has two commitments: (a) a remote job entry station communicating via telephone lines to the large control computer on the University's main campus over fifty miles away and (b) an on-site small computer especially well suited for use in acquiring data from and controlling the operation of laboratory instruments. The combination of these two types of computer systems gives this new medical school ample capability without committing it prematurely to any given large-scale facility. In a rapidly developing scientific environment such as this, the flexibility offered by the current computer resource planning will almost certainly be an important factor in bringing this young institution quickly and smoothly up to its full potential.

Digital Computation II: Rutgers University

Unlike the first new resource, the emphasis at this resource is upon concepts rather than instrumentation. That is, this resource's principal focus is the aggregate expertise of its staff in the area of model building and artificial intelligence. The resource's goal is to make these skills available to biomedical scientists in the eastern United States and, in so doing, to identify research topics for further elaboration of those aspects of these computer methods which seem to have biomedical import. While this resource is somewhat analogous to others where major foci are image processing or biomathematics, it nevertheless does represent the first of its kind ever established and will be the subject of considerable attention by DRR staff and the members of the biomedical computing community as a possible model for comparable endeavors elsewhere.

Mass Spectrometry: Stanford University

The BRB's newest initiative in this area also has the distinction of being the first instance of its new class of award--the resource-related research project grant. In this case the mass spectrometry facility at Stanford University (not itself a BRB-sponsored center) will be the setting for a project involving the application of artificial intelligence methods to the interpretation of the mass spectra of steroids. This represents the first attempt to place a sophisticated analytical instrument under the control of a complex problem-solving computer system and, if successful, will do much to enhance the capabilities of the mass spectrometric facilities not only at Stanford, but throughout the Nation.

Nuclear Magnetic Resonance: University of Utah

This resource will be concerned specifically with the detection of the stable isotope of carbon (C^{13}) in natural abundance. Once this can be done routinely, biomedical investigators in the intermountain region will have almost unprecedented opportunities to directly study conformational changes of molecules in solution--such as those which are known to occur during enzyme/substrate interations--without having to undertake the often arduous task of preparing isotopically enriched versions of these molecules.

Electron Microscopy: University of Colorado

This resource will provide the Nation's second one-million volt instrument dedicated to biomedical research (the first being the BRB-sponsored installation now under construction at the University of Wisconsin). The Colorado resource will provide scientists in the western United States with a unique facility

for examining thick-sectioned biological material, and it should be especially valuable for studies of chromosomes, tubular systems within cells, and basic skeletal muscle structure. This resource, along with the Wisconsin center, will soon provide ultrastructural scientists in the United States with the research opportunities their counterparts in England, France, and Japan have been enjoying for several years.

RESEARCH CONTRACTS

Over the past several years the research contract has become a powerful complement to the BRB's grant activities. The contract mechanism has been employed to support two kinds of projects: (a) projects which are designed to produce the scientific, technical, and managerial information necessary to plan effectively for various types of resources and (b) projects which are designed to insure that the products of resources' technological innovation are put into application in other research settings as well as those of their origin. The current state of such contract-supported efforts is summarized below.

Provision of Mass Spectrometry Services on a Regional Basis

One of the major unresolved managerial problems associated with mass spectrometry resources has been eased considerably as a result of a contract with the Battelle Memorial Institute. Battelle undertook a study of how, if at all, high resolution mass spectrometry capability could be provided to biomedical investigators in a broad geographical region on a "pure service" basis, i.e., with only a modest amount of consultation about sample preparation, spectra interpretation, and the like, and with essentially no research collaboration. Battelle demonstrated that it was able to identify and put into practice the technical and administrative mechanisms needed to provide such service and has provided BRB staff and the community in general with some valuable insights as to how this type of mass spectrometry service might be established in other settings. As part of this study mass spectrometry services were made available to approximately 80 scientists representing every region of the country and, even more important, having financial support from almost every NIH institute. The project is planned to continue with special emphasis on the class of problems involving the identification of molecules in human tissue fluids.

Evaluation of a Display-Oriented Computer Terminal

The rapidly advancing technology of computer graphics has captured the attention of many biomedical scientists in recent years. This is hardly surprising, given the ubiquity of charts, graphs, and other forms of two-dimensional data in their areas of research.

In response to this need, many of the BRB-sponsored computer resources have elected to undertake research and development involving display methods.

In the case of the Biotechnology Resource at Loma Linda University, the result of the core research was a new display terminal--an instrument designed specifically for the requirements of the resource's users. Early studies using this terminal at Loma Linda proved sufficiently encouraging to BRB staff and advisors to suggest that other settings be provided the opportunity to work with it. This exportation was accomplished by letting a contract with the University of Iowa to prepare production versions of eight of these devices and by soliciting competing proposals from other organizations who wished to experiment with one or more of them. During the latter part of FY 1971 the evaluation efforts went into full-scale operation with the award of terminals to Stanford University, the University of Washington, the University of California at Santa Barbara, the University of Minnesota, and Duke University.

Preliminary Experience With a High Voltage Microscopy Resource

As part of its efforts to determine the overall biomedical utility of high voltage electron microscopy and the nature of the role the DRR should play in this area, BRB staff have contracted with United States Steel Engineers and Consultants, Inc., to provide qualified biomedical scientists limited access to the only one-million volt instrument currently in this country. The goal is to make possible a sufficiently rich selection of research experiences to help the staff and its advisors sharpen their expectations as to the eventual impact of this new technology and to define the management practices required to operate such a large-scale installation most effectively. The timing of this contract is such that a significant number of scientists will have had opportunities to work with this type of instrument by the time the facilities at the Universities of Wisconsin and Colorado are ready to initiate full operations.

A Prototype Resource for Biochemical Reaction Kinetics

One of the areas under consideration as a theme for a new modality of Biotechnology Resource is biochemical reaction kinetics. In recent years there have developed a family of instruments capable of following the course of chemical reactions in the millisecond and nanosecond ranges. It seems clear that such instruments have much to offer toward the elucidation of such fundamental life processes as the loading and unloading of oxygen by the hemoglobin molecules in the blood.

In recognition of the above the BRB staff has raised the corollary question--Is the resource grant mechanism an appropriate vehicle for sponsoring work in this application area? To achieve at least a tentative answer, plans are being completed to have a contractor who already possesses the necessary facilities function as a resource in support of qualified scientists throughout the Nation. This project should be an efficient and economical way to develop information to assist DRR's program planning in this area.

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Annual Report
Chemical/Biological Information-Handling Program
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Introduction

The Chemical/Biological Information-Handling Program aims to strengthen the predictive aspects of pharmacology and medicinal chemistry by exploiting the most modern available computer-based information-handling techniques in a discipline-oriented computer system. Through the contracts mechanism, a coordinated program of demonstration projects, long-term basic artificial intelligence research, and large-scale information system design, implementation and operation has been carried out or is in progress. The resulting system, dedicated to use by the pharmacology and medicinal chemistry community, will function as a powerful tool in conjunction with standard archival information services and general-purpose institutional computer systems.

Steps Toward Implementing Program Philosophy

The basic program philosophy of the CBIH Program, elaborated in greater detail in the last two annual reports, centers on the provision of logistical and cognitive aids to laboratory researchers in pharmacology and on the facilitation of mutual interaction by the most modern and useful means possible among these researchers. The CBIH Program does not intend to compete with large-scale data base and document retrieval systems, but rather is striving to assist the individual scientist in obtaining the most information from his own data and that of his collaborators. The first steps in this program have been taken with the implementation and evaluation of a selected subset of the information-handling commands contained in the design for PROPHET, the central effort of the CBIH Program. In an operational environment, PROPHET will be a dedicated, time-shared computer system accessible over ordinary telephone lines by researchers using graphics terminals anywhere in the Nation. Its set of information-handling commands will provide for manipulation of both chemical and biological data and will permit an individual scientist to operate in his own data management style, subject only to built-in standards necessary to insure ease of communication of data and programs among various PROPHET System users.

Elaboration and Implementation of PROPHET Specifications

The technical assistance contractor to the CBIH Program, Bolt Beranek and Newman Inc. (BBN), is continuing its elaboration and implementation of the design of the PROPHET System, a job which now dates about three years in progress. Information-handling commands essential to pharmacologists, such as picture-displaying, table-handling, and molecule-handling commands, have been demonstrated. Other parts of the original PROPHET design less essential to a basic system, such as graph-handling commands, have not been implemented yet. Concern that the size of the programs already written for PROPHET may be too large to permit acceptable response speed in an interactive time-shared

system has caused some of the BBN's efforts to be diverted to making more compact and efficient sections of the PROPHET System already implemented.

Selection of a Host Institution and Operations Contractor for the Computer Facility Dedicated to PROPHET

In addition to implementing parts of the PROPHET System design, BBN aided the staff of the CBIH Program in selecting a computer for use in the CBIH dedicated facility. Concurrently, CBIH Program staff and the CBIH Review Committee began the task of selecting an operations contractor to install the hardware on its site, implement the hardware and software in accordance with specifications provided by CBIH Program staff, advisors, and BBN, and operate the computer facility in a service-oriented manner.

The standard administrative procedures for eliciting proposals were followed: announcement in the Commerce Business Daily, elimination of clearly unqualified respondents, solicitation of proposals (RFP), evaluation of proposals received. It is anticipated that one organization among four entering proposals will be selected before the conclusion of the fiscal year, and that the computer facility will be operative in early autumn of 1971.

Collaboration with Research Scientists

The CBIH Program took the first steps toward collaboration with research pharmacologists during the fiscal year 1971. At this stage of the development of the PROPHET System, any interaction between other scientists and the CBIH Program would be considered as collaboration, rather than service to the scientists, as the set of commands available at present is incomplete and subject to revision based on comments received during interactions with the computer-naive pharmacologists. The experience of dealing with different groups of research scientists in the field and of eliciting from them their reactions to the PROPHET System design has been illuminating. Particularly important has been the recognition of the diverse modes of data collection and experimental design and analysis in which different pharmacologists operate. Collaboration with different scientists affiliated with the National Cancer Institute, either intramurally or extramurally, has revealed information manipulation needs ranging from organization and analysis of large volumes of drug effectiveness and toxicity data, to rather sophisticated mathematical modeling requirements. These interactions have been valuable in confirming or overturning design assumptions used in developing the specifications for PROPHET, and their continuation will shape the future growth of the Program.

PROPHET-Related Demonstration Projects

Problem areas relating to three fundamental aspects of the PROPHET System have been explored during the fiscal year by four demonstration projects funded under contract with the CBIH Program.

The graphics orientation of PROPHET is reflected in projects at Columbia University and Harvard University. The study at Columbia has continued past work in displaying and manipulating three-dimensional representations of molecules, including relatively large proteins. Molecule conformation analysis

is also included in the Columbia development package. The Harvard group has extended the abilities of a chemist by means of graphic stylus input to interact with a computer program analyzing organic synthesis mechanisms and to display results of these analyses.

At the RAND Corporation, a rather general mathematical model exerciser and an interface between this exerciser and a wide class of biological/mathematical models has been developed. The scholarly review of the biomathematical modeling literature and the careful design effort of the exerciser and interface have greatly affected the thinking of other components of the CBIH Program on the problem of incorporating and using mathematical models in PROPHET (more on the use of mathematical models is included below).

One of the principal aims of the PROPHET System is to facilitate communication among researchers. A study sponsored at Pomona College has looked into the problems of nomenclature within data files of medicinal chemistry interest, and into the problem of transferring computer programs and data results in that field. As the PROPHET System grows, it is expected that the public data base will increase in size, and the results of the Pomona study will assume great importance.

The Use of Mathematical Models for Knowledge Management - Toward a Predictive Science

As set forth in the CBIH Program Annual Report for FY 1970, a continuing long-range goal of the PROPHET System is the development of computer capabilities for handling, organizing, and deriving useful conclusions from biological data. Significant progress toward achieving this goal is being made by the CBIH project at the University of Pittsburgh. At the beginning of the fiscal year, the team of pharmacologists and computer specialists working in Pittsburgh had developed an accurate model of the subcortical neurological mechanisms controlling skeletal muscle movement, and had the capability of altering, exercising, and examining the model under either manual or automatic (computer program) control. Relatively straightforward questions concerning the affects of such operations as the applications of well-characterized drugs or specific surgical procedures could be answered by the executive program supervising the model.

Starting from that point, the University of Pittsburgh investigators during the past year have been working toward a far more general realization of inferential information-handling techniques by computer for use in pharmacology and medicinal chemistry. The aim of the project is to use mathematical models as "theories" of drug actions (for example). Given known facts about a drug, a theory in the form of a model may be used to generate answers to specific questions, rather than retrieving answers from a tightly structured data base. True computer/investigator interaction would result from this mode of operation: predictions of drug action would be based on the answers generated by the model, and verification of these predictions would be used to check and revise the structure of the model. It is intended in the future to develop the capabilities of the computer to the extent that it might suggest the relevant experimental verifications to be tried.

As the inferential information-handling techniques within the PROPHET System become more sophisticated, a host of questions is introduced, dealing with the problems of perceiving different levels of resolution of a model, of maintaining consistency between various models of a particular physiological/pharmacological system, of providing easily used reference and exercising capabilities to the non-programmer, and of insuring ease of communication of models and data among different investigators using the PROPHET System.

These questions are being addressed by a coordinated effort involving the University of Pittsburgh group and the staff of Bolt Beranek and Newman Inc. Out of this coordinated effort, the CBIH Program hopes to define those properties fundamental to useful biological models and to derive from this set of properties an array of computer model-building, exercising and examination tools which will be of general usefulness in a graphics-oriented service-mode computer to be run by the CBIH Program. Among those capabilities already foreseen is that of drawing in a network model on a graphics display and being able to specify the types of nodes in the network either explicitly, or as a standard "library" type, or as a part of another model (perhaps that of a different investigator).

An example of BBN/Pittsburgh interaction involves a model of the distribution of seco-barbital in the rabbit. Developed in Pittsburgh, this model has been used there not only as a test base for model-building tools but also as an aid in laboratory investigation. Characteristics of laboratory data not explained by the clinical investigator's original conception of drug flow (as expressed in the original model) were explained by alterations in the model easily carried out by the computer specialists. These alterations were verified by subsequent laboratory analysis which revealed an entero-hepatic circulation of seco-barbital in the rabbit not previously recognized. The BBN group has used the Pittsburgh experience to select various model construction and organization techniques and to recognize certain limitations in the perception (control and output) characteristics of the Pittsburgh modeling system, suggesting more realistic requirements.

The integration of the efforts at Pittsburgh and BBN is one of the major steps begun in the fiscal year. The promise of developing "intelligent" mathematical models of pharmacologically relevant systems, with full comand of PROPHET's information-handling tools, and accessible via easy to use graphics capabilities, is a truly exciting one for the task of setting pharmacology on a firmer predictive foothold.

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Fiscal Year 1971
Annual Report
General Clinical Research Centers Branch
Division of Research Resources

I. Introduction and Goals of the Program

Since the inception of the General Clinical Research Centers Program, the primary goal has been to provide to clinical investigators in widely scattered geographic locations the specialized resources and facilities necessary for the conduct of excellent clinical research. Traditionally, support has been provided for a fixed number of hospital beds in a discrete geographical area staffed by specialized nursing, dietary, and laboratory personnel. These units have functioned as institutional resources available to all qualified investigators within the parent institution for use in studying patients admitted as part of approved research projects.

Despite stringent budgetary constraints in recent years, the Program continues to support the best available resources for clinical research. Two-thirds of all hospital beds in the nation specialized for research on human subjects are supported by this program. The number of scientific papers published each year has continued to increase progressively despite severe reductions in awards to each existing Center in the past few years. The total output of original scientific articles for 1967 was 1,477; this increased to 1,982 in 1968, to 2,068 in 1969, and to 2,315 in 1970.

During the past two years, over half (41) of the Centers have been reviewed on site, and detailed analyses have been made of a number of the components common to all centers within the Program. From this body of information, a number of mechanisms by which the Program may be further improved have been initiated or are now under active discussion.

Access to these centers has enabled investigators to translate new knowledge into early clinical application. In addition, these centers have been an essential resource for general medical and paramedical training programs.

The original concept of a Center as a geographically and physically discrete inpatient unit has slowly evolved over the years in response to the changing needs of the nation's clinical investigators. The concept is now being extended beyond the research limitations of a solely inpatient unit to include facilities and personnel necessary to incorporate an outpatient or ambulatory clinical research program. The additional latitude provided by this extension represents an important complement to inpatient studies.

The GCRC program grew at an almost constant rate between 1960 and 1967. In the past few years, rapidly rising costs and fiscal restraints have prevented expansion and have forced support for fewer centers and a decreasing number of beds. Table I depicts this program history.

Table 1. GCRC Program, FY 1960 - 1971

Fiscal Year	Institutions	Medical Schools	Centers Awarded	Funded Beds	Apportionment in millions of dollars
1960	8	8	8	-	3
1961	31	30	32	142	8
1962	50	46	56	404	27
1963	59	51	66	566	30.9
1964	66	56	77	758	27.1
1965	70	58	82	891	26.9
1966	74	61	88	998	28.5
1967	75	62	91	1,056	28.5
1968	75	62	91	1,051	30.4
1969	77	64	93	1,023	35.0
1970	77	64	93 1/	904	35.0
1971	71	54	80	862	38.0

1/ In 1970 fiscal constraints necessitated a phase out budget to eleven centers and two children's centers were amalgamated with an adult center at the same institution so that in 1971 about 80 centers will be active.

II. Geographic Distribution

The GCRCs have become a focal resource for the majority of the Nation's leading institutions; 81 centers in 71 medical institutions in which over 2,000 medical scientists admit patients for study.

Using a geographical alignment of states based on population census, Table 2, it is readily apparent that the distribution of centers, beds, and direct costs for fiscal 1971 generally parallels population concentrations. It can be seen that the number of beds provided by GCRCs generally parallels the population of a state. There are some exceptions, however, which could probably have been predicted inasmuch as geographic distribution of GCRC beds has not been of prime concern in determining which center was to be funded. Exceptions referred to above are New York and Wisconsin (in the >10.0 million population category); Massachusetts (3.0 - 9.0 million); Colorado and Utah (1.0 - 3.0 million); and Washington, D.C. and Puerto Rico (1.0 million). It is within reason that future awards to new institutions might consider population data, especially when other scientific factors are somewhat equal. For example, if a choice had to be made between two states (Illinois and Pennsylvania), each having an application of somewhat equal merit, an award should probably be given to Illinois.

Table 2

RELATIONSHIP OF POPULATION TO NUMBER OF GCRC BEDS AND NUMBER OF CENTERS IN STATES HAVING GCRCs

STATE	POPULATION* (in millions)	NO. OF APPROVED GCRC BEDS	NO. OF GCRC CENTERS
California	20.0	73	7
New York	18.2	154	11
Wisconsin	14.4	12	1
Pennsylvania	11.8	60	8
Texas	11.2	43	4
Illinois	11.1	32	4
Ohio	10.6	48	6
Michigan	8.9	26	2
Florida	6.8	24	2
Massachusetts	5.7	84	6
North Carolina	5.1	37	3
Missouri	4.7	39	2
Virginia	4.6	20	2
Georgia	4.5	10	1
Tennessee	4.0	31	2
Maryland	3.9	33	2
Minnesota	3.8	11	1
Washington	3.4	22	2
Alabama	3.4	10	1
Connecticut	3.0	16	1
Iowa	2.8	10	1
Oklahoma	2.6	10	1
Colorado	2.2	24	2
Kansas	2.2	6	1
Oregon	2.0	4	1
Arkansas	1.9	8	1
Utah	1.0	15	1
District of Columbia	0.8	24	2
Vermont	0.4	6	1
Puerto Rico	-	12	1
30 States		904	80

*1970 Census, Bureau of Census, U. S. Department of Commerce

III. Training

Within the Centers, senior scientists, research fellows, and house staff are exposed to increasingly sophisticated methods and concepts of clinical research. Such training is essential for continued development of competent investigators and for improved medical care in the Nation. In these Centers, future medical practitioners develop foundations of knowledge that facilitate critical evaluation of new medical discoveries with which they will be confronted in the course of their careers. In addition, the Centers assist in the training of large numbers of paramedical personnel. They are the primary hospital facility in which nurses, dietitians, and laboratory technicians gain practical experience in newly developed patient care techniques, generally resulting in better quality of hospital care. The table below shows the numbers of individuals who received training in clinical centers in the past seven years.

Table III. Training in GCRCs

Fiscal Year	Medical Students	Interns	Residents	Fellows
1964	582	288	568	579
1965	1,060	362	937	791
1966	1,684	609	1,261	1,190
1967	2,178	682	1,398	1,104
1968	2,538	863	1,576	1,227
1969	2,937	1,019	1,852	1,325
1970	2,614	912	1,707	1,331

IV. Fiscal Summary

The distribution of beds and funds by center size in fiscal 1971 is given in Table IV. It can be seen that the average cost per patient day is much higher in the small centers and that the most efficient operation, assuming equality of scientific effort, seems to be in larger centers where the number of funded beds is eighteen or more.

Figure I provides, in graphic form, the history of program appropriations and expenditures in relationship to the program ceilings recommended by NARRC (National Advisory Research Resources Council). After an initial period of five years where appropriations were more than adequate to meet expenditures recommended by the NARRC, the last few years have seen recommended expenditures outstrip each year the appropriation available to the program.

Figure II gives a history of all expenditures over the years, with a breakdown related to personnel, hospitalization, renovation and equipment and other expenditures. It is obvious that personnel and hospitalization costs have become and continue to be the key factors in rising costs of the program, despite the fact that the number of centers and the number of active beds supported have been forced into a steady decline.

Table IV

GENERAL CLINICAL RESEARCH CENTERS

Distribution of Beds and Funds By Center Size
Fiscal Year 1971

Number of Beds	Number of Centers	Number of Funded Beds	Funded Patient Days	FY 1971 Funded* (Direct Costs)	Average Cost* Per Patient Day
Total	80	862	238,227	$35,187,058	$147.70
4-6	19	107	28,750	5,093,437	177.16
7-9	13	103	27,229	4,358,022	160.05
10-11	18	180	50,874	7,147,927	140.50
12-14	12	147	39,824	5,674,124	142.48
15-17	7	102	27,610	4,090,572	148.16
18+	11	223	63,940	8,822,976	137.99

Indirect Cost - FY 1971 Funded $1,941,488 and Average Cost Per Patient Day - $ 8.15
Total Budgeted - FY 1971 Funded $37,128,546 and Average Cost Per Patient Day - $155.85

Figure II

General Clinical Research Centers

History of Expenditures Under the General Clinical Research Centers Program,
by Selected Budget Categories
Fiscal Years 1961 - 1969

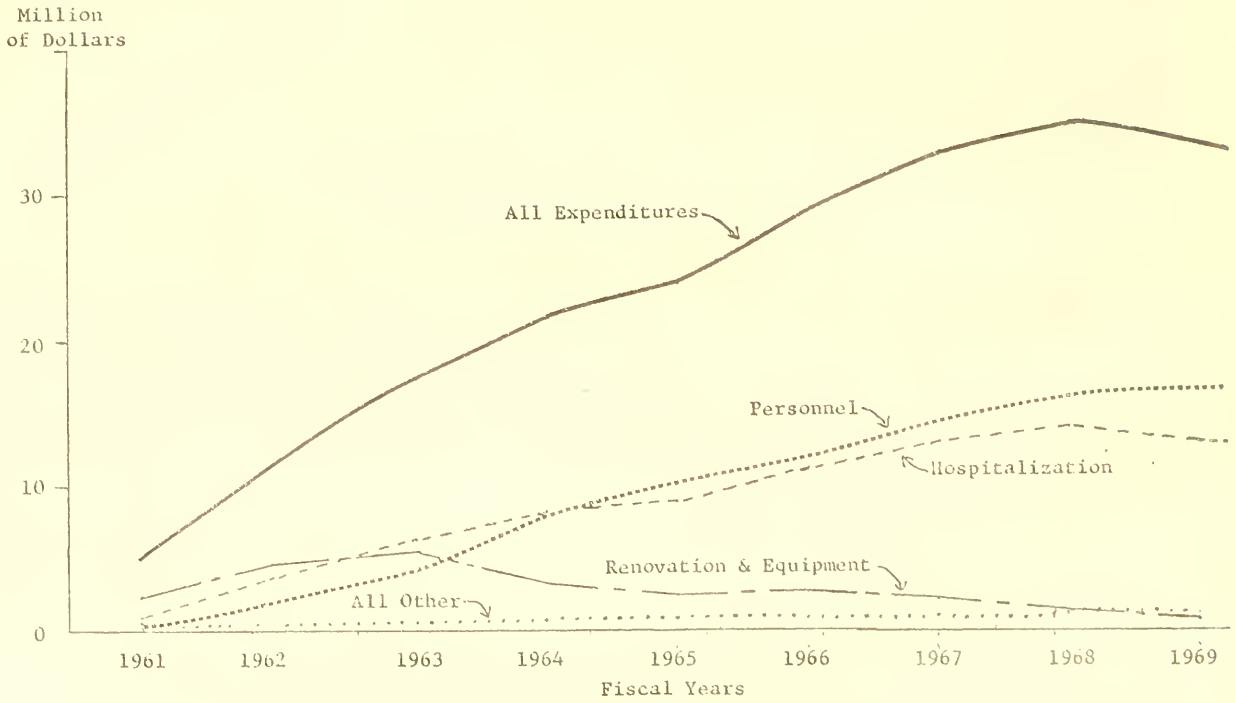
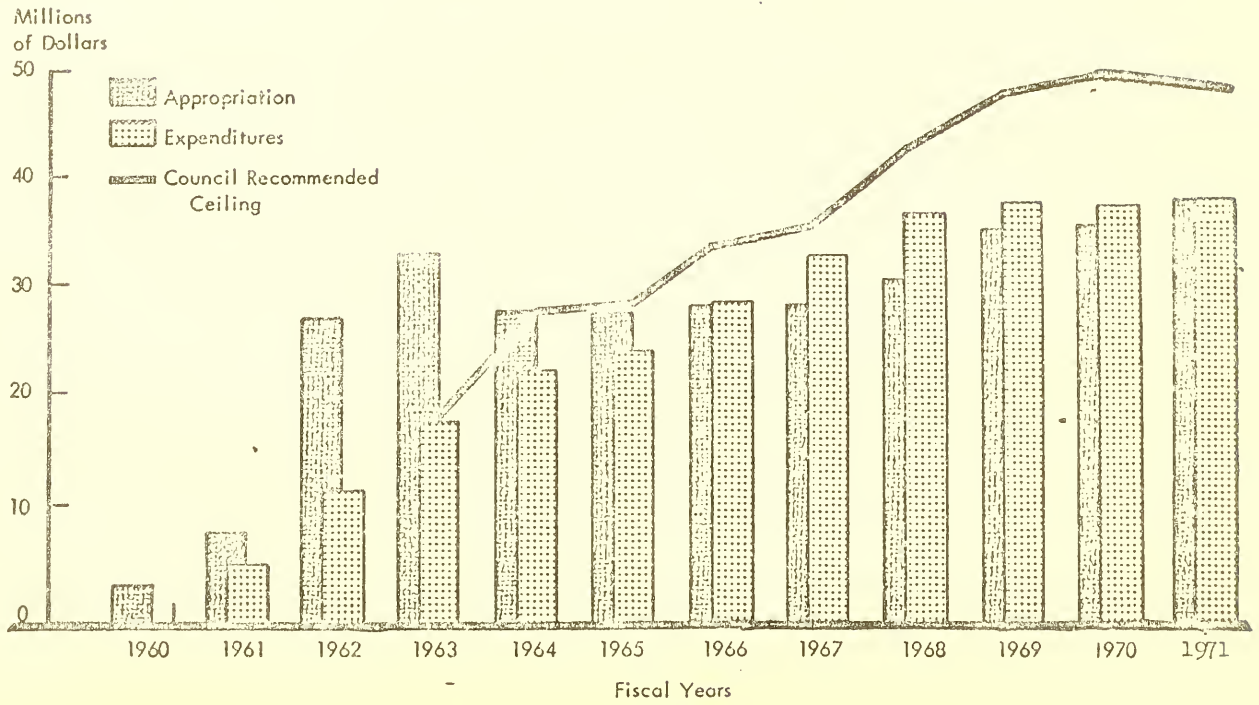


Figure I

General Clinical Research Centers

History of Appropriations, Expenditures, and Ceilings Recommended by the National Advisory Research Resoures Council for the General Clinical Research Centers Program Fiscal Years 1960-1971



V. Program Highlights

As noted previously, investigators have used centers for the study of virtually all aspects of human disease. The scope and vigor of the supported clinical research is demonstrated below in the following ways: (a) by showing the number of patient days and dollars spent in several representative major disease categories; (b) by presenting scientific highlights, the summaries of which were submitted by individual centers as examples of promising work in progress; and (c) by giving a few examples of how a GCRC can benefit local communities.

a. Representative Major Disease Categories[1/]

Study Categories	No. of Studies	Patient Days	Amts. Expended 1968-1969
Sickle Cell Anemia	5	271	$ 38,479
Genetic Studies	285	18,086	2,568,031
Hepatitis	12	573	94,139
Reproduction and Population	211	14,661	2,081,715
Cancer	177	15,091	2,142,771
Heart	230	18,428	2,616,592
Child Development	716	48,923	6,946,577

1/ Disease classifications overlap in some instances

b. Scientific Accomplishments

During the year ending September 30, 1970, over 3,320 investigators conducted research protocols on 93 General Clinical Research Centers. Their work resulted in the publication of 2,315 papers and 1,077 abstracts. Although the number of researchers actually involved on the Clinical Centers has decreased during this past year by comparison to 1969 totals (due to budgetary constraints and the phasing out of 13 Clinical Centers), the total number of research publications increased approximately 15 percent over those of the preceding year. The following highlights a few of the major areas of interest and accomplishments among the Centers.

Human Organ Transplantation

Within the past decade, human organ transplantation has become a reality. Much of the original research relating to renal transplantation was done on Clinical Centers throughout the country. Transplantation and related problems have remained a major interest for clinical investigators involved in the Clinical Centers Program.

Researchers at the Boston City Hospital and the Clinical Center at the University of Florida are actively involved in investigating various methods for improving the survival rate of corneal transplantations. The cornea is the completely clear, thick membrane which covers the front of the

eye and which allows light to enter the eye, go through the pupil, the lens, and then be perceived in the retina. Many diseases, as well as injuries, infections, and inflammations, leave a permanent clouding and scarring of the cornea. Many thousands of people have become blind because of this. At the University of Florida, a technique has been developed by which corneas can be taken from people after death, can be quick frozen, and can be indefinitely preserved. These corneas, if transplanted, in a high percentage of cases will become perfectly functional and will allow the patient to be able to see. The development of this storage technique has been of extreme importance in supplying a constant supply of such tissue for transplantation. At the Boston City Hospital, they are studying the efficacy of immunosuppressive therapy in patients receiving corneal transplants, and have achieved more lasting and higher quality grafts.

At the University of Arkansas, another aspect of transplantation has been studied. Through the newly developed technique of using skin micrografts, they are evaluating the rejection phenomenon in untreated subjects. They have discovered that by pretreatment of the micrografts with various chemical agents prior to implantation, significant prolongation of transplanted skin can be accomplished without the use of immunosuppressive drugs. In addition to these Centers cited, many other Centers are actively involved in continuing their research efforts in human organ transplantation.

Genetic Studies

Clinical investigators have been aware for many years that a majority of the causes of mental retardation and perinatal and neonatal morbidity and mortality are attributable to genetic defects. Through the techniques of amniocentesis (removal of fluid from the sac surrounding the human fetus) and culturing cells obtained from patients' tissues, researchers are gaining insight into detection of basic defects in the function of growing cells and in the diagnosis of genetic defects. A major area of interest in a number of Clinical Centers has been detecting and studying these so-called genetic defects. At Cornell University Clinical Center, researchers are using cell cultures to identify 1) the genetic mucopolysaccharidoses; 2) Marfan syndrome and other connective tissue disorders; 3) cystic fibrosis, and 4) genetic neurological disorders. The initial steps in these studies have been to identify affected family members and to establish cultures of their cells. By studying these cells, researchers hope not only to identify affected family members and "high risk" pregnancies, but also to determine what the basic biochemical defects are in these inherited disorders, and possibly develop techniques for treatment. At the University of Chicago Clinical Center, these cell culture techniques are being used to identify not only the children with various lipid storage diseases which lead to mental retardation, but also to identify "carriers" of these disorders without clinical evidence of the disease. Identification of the latter subject is of extreme importance in genetic counseling for the prevention of these diseases. Both Duke University and New York University researchers are studying amniotic cells obtained by amniocentesis to diagnose *in utero* various genetic disorders. By studying these cells, they hope to determine

the biochemical properties of the abnormal enzymes in a number of inherited disorders in hopes that these studies may lead to a new type of therapeutic intervention to correct enzyme deficiencies or defects.

Metabolism

A great many of the studies conducted on the Clinical Centers have been devoted to the broad field of metabolism. These studies cover a spectrum including actions of thyroid hormone, insulin metabolism and its relationship to the etiology and causes of diabetes, the effect of dietary fat on incidence of vascular disease, etc. Recent studies at many Centers have given further indication that diet may have a profound effect upon the incidence of vascular disease which leads to the early incidence of heart attack and stroke. Researchers at many Centers are studying the effects of diet and various modes of therapy on lowering serum cholesterol and triglyceride levels in patients with predispositions to early vascular disease.

It is known that in American women, pregnancy causes a rise in serum cholesterol level. This increase has been attributed to hormonal changes in pregnancy and is of concern because of its possible relationship to the development of gallstones and coronary heart disease, diseases more common in women with multiple pregnancies. At the University of Iowa, researchers have demonstrated that with proper dietary control, including removal of cholesterol from the diet, lowering of serum cholesterol concentrations can be accomplished in pregnant women. They have concluded that the restriction of dietetic cholesterol can reduce, and may prevent, the usual elevation of serum cholesterol experienced during pregnancy. They hope to demonstrate that this reduction may help to decrease the incidence of gallstones and coronary heart disease in multiparous women.

Muscular Dystrophy

There are several types of muscular dystrophy, but all involve a wasting of muscles. The consequences of this disease may be devastating, leaving a child deformed or virtually immobile. At the University of Chicago, researchers have discovered that female hormones may have a therapeutic benefit in this disease. Based on evidence that the progress of this disease seems to be more rapid and the muscular weakness more profound in men, trials of therapy with the synthetic female hormone, diethylstilbesterol, have shown that approximately half of patients treated thus far have experienced marked improvement. These results will be extended and further information may lead to the subsequent development of a new management program. At the University of Iowa, they have demonstrated that the most common type of muscular dystrophy, III A, is an almost exclusively male disease and is usually transmitted to the male through his mother's genetic contribution. The causes of muscular dystrophy are unknown except that it is caused by an abnormal gene. Although the "carrier" of the defective gene has no apparent symptoms, tests can be made to determine if the mother is indeed such a "carrier." In the past, identification of this

"carrier" state has been determined by blood enzyme and muscle tissue examination but these methods have been largely unreliable. A group of biochemists and pediatricians at the University of Iowa have developed a new method of detecting the "carrier" state with much greater accuracy than before.

Endocrinology

In recent years, it has been shown that an area of the brain, the hypothalamus, secretes hormones which act on the pituitary gland, stimulating it to release other hormones. The pituitary hormones in turn stimulate the thyroid, adrenals, ovaries, and testes to produce their respective hormones. In the past several years, investigators have been frustrated by an inability to isolate and identify these hypothalamic hormones. However, within the last year, scientists at Baylor University, using the Clinical Research Center, have succeeded in isolating and synthesizing one of these hypothalamic hormones, thyrotropin releasing factor (TRF). Scientists at three different centers, Baylor, Northwestern, and the University of Alabama, have shown that TRF causes an immediate and dramatic rise in the blood concentration of the pituitary hormone, thyrotropin, or thyroid-stimulating hormone (TSH). At Northwestern University, it has been shown that patients with pituitary disease states often exhibit a decrease or absence of responses to TRF. Thus, TRF may provide the basis for precise, safe, and highly sensitive tests for the early diagnosis of obstructive lesions of the pituitary gland.

Cancer

Extensive research in cancer and the causes and treatment of cancer have continued over the past several decades. Recently, researchers have gained additional information which seems to implicate the role of viruses in human cancer. In addition, scientists are becoming aware that the host's ability to respond to abnormal tissue growth may play a key role in the development and extension of malignancy. At the Roswell Park Clinical Research Center, patients with Hodgkin's disease are being studied. This disease is characterized by the malignant enlargement of lymph nodes, spleen, and general lymphoid tissues, with ultimately fatal spread to other organs of the body. It is well known that these patients have immunologic defect related to the thymus gland function. At Roswell Park, several patients suffering from Hodgkin's disease have received human fetal thymus gland transplants and over half have achieved a return to immunologic responsiveness. Follow-up of these patients is required in order to evaluate the value of this operation for the long-term control of this disease.

Recent studies have revealed that patients with several types of cancer have in the blood stream both circulating antibodies and circulating sensitized lymphocytes (white blood cells) which specifically attack cancer cells. Laboratory analyses have shown that the ability of a patient's lymphocytes to destroy his cancer cells is significantly increased by prior activation of these lymphocytes with the chemical substance, phytohemagglutinin.

Preliminary reports at the University of Colorado Clinical Center suggest that parenteral administration of phytohemagglutinin to cancer patients may sensitize lymphocytes within the patient's body and produce favorable responses in terms of blocking tumor growth and spread; however, the repeated systemic use of this substance is limited by the development of antibodies in the body against it. At this Center, they have recently developed a procedure by which large numbers of lymphocytes may be removed from the body and then activated with the phytohemagglutinin. These activated lymphocytes can they be reinfused in the patient. A majority of the patients to whom this technique has been applied have developed a definite and encouraging reduction in the size of their tumors.

Virology

Viral infections and epidemic influenza cause a large number of deaths and are responsible for tremendous losses related to job absences. Vaccination against epidemic strains of influenza is difficult because the epidemic is usually caused by a new strain of virus against which effective vaccines are not readily available. Unfortunately, new vaccines which can be developed against epidemic strains of influenza usually may be produced at a rate too slow to effectively immunize the population against the epidemic. At the Clinical Center at Methodist Hospital in Houston, Texas, researchers are field-testing a new vaccine which may be rapidly manufactured and is equally effective to traditional types of vaccine in terms of antibody response elicited and the protection it affords. This type of vaccine is manufactured by combining the epidemic strain of virus with a rapidly growing laboratory strain of virus. A new vaccine can be made within two weeks. This will allow immunization of most, if not all, of the population at the arrival of the new strain of epidemic influenza.

Growth and Development

For the past decade, the majority of clinical research in the United States on childhood growth has been conducted in General Clinical Research Centers. The use of human growth hormone from cadaver pituitary glands in the clinical investigation and therapy of hypopituitary dwarfism was initiated in Clinical Research Centers, and these Centers remain the primary facilities in the nation where HGH is presently being investigated clinically. Investigators using Clinical Research Centers were among the first to recognize the distinction between true premature infants and those of low birth weight due to intrauterine growth retardation. The distinction is of paramount importance in that the postpartum complications and the appropriate methods of management for the two types of small newborn are often critically different. Many clinical studies have demonstrated that newborns, like older children, tend to behave more in keeping with their age than with their size. Charts illustrating normal muscle tone and the normal developmental appearance of various neuromuscular reflexes in the full-term baby have been developed by a General Clinical Research Center. These charts are now available to physicians throughout the Nation and are used in the delivery

room to enable obstetricians and pediatricians to distinguish clinically between the premature and the growth-retarded infant. The same Center has also demonstrated that electroencephalographic tests can evaluate the response of the normal full-term baby's brain centers to visual and auditory stimuli and distinguish the full-term intrauterine retarded infant from the true premature.

A large number of the investigations relating the state of childhood nutrition to mental development have been and continue to be conducted in General Clinical Research Centers. Investigators are accumulating evidence that the problem of obesity which plagues many middle-aged Americans may actually be the result of overfeeding during infancy with a resulting early development of fat cells which throughout life have a propensity to become filled and remain filled with fat.

In addition to the above, a considerable quantity of work continues on the research centers detailing the effects of nutrition, hormonal balance, emotion, disease, and inheritance on the processes of growth and development in children. As noted, in addition to the immediate application of this information to remedial therapy in affected children, the information may have larger application in aiding scientists to understand and possibly avert some of the adverse effects throughout life of aging.

Computer Technology

Within the past decade, the computer technology field has undergone tremendous expansion. Several attempts have been made to apply computer resources to medical care problems; however, the primary thrust has been toward development of computer capabilities for "hospital information systems" or "health care delivery systems." The specific use of computer resources for clinical investigation has lagged far behind these other developments. However, within the context of the General Clinical Research Centers, new and exciting applications of computer technology to clinical investigation have taken place. At the Stanford University clinical center, researchers are attempting to explore the biological activity of hormones. They are using computer facilities to discover distribution patterns and actions of various hormones. They have found that nonmathematical, or noncomputer, techniques in biological research cannot envision the many interrelationships of the various body compartments. The methodology of systems analysis making use of computers can determine the interrelation between hormones and the human body and can further be extended to distinguish between diseased humans and so-called normals.

At the Massachusetts Institute of Technology researchers have developed an entirely computerized Clinical Research Center in which patients admitted for study are automatically placed on predesigned computer research protocols. Laboratory and other pertinent data are then stored on tape and analyzed with particular emphasis on pertinent parameters. Such a setup may serve as a prototype for future patient care centers and clinical centers throughout the country.

At another center, collaborative studies with computer engineers have led to a systems analysis approach to the study and care of critically ill patients. Researchers have been applying computer techniques and have developed better tools for analyzing metabolic, physiologic (particularly cardiovascular), and clinical data for obtaining multivariable physiologic evaluation using high dimensional statistical techniques. An attempt has been made to interpret data and return them almost immediately in a form which can be used for the management of critically ill patients by an experienced physician. As a corollary to this approach, an attempt has been made to develop a series of computer programs to assist in the management of patients' fluid and metabolic requirements during the period of acute stress. These programs are also integrated with the clinical information according to the clinical decision-making logic so that they can provide a kind of "living textbook," which can help to instruct the doctor in the therapeutic precautions and in suggestions for management.

Parkinson's Disease

Parkinson's disease is characterized by progressive stiffness of body muscles and tremor. It is a disabling disease affecting large numbers of elderly people. Within the past two years, two new drugs have become available which will vastly improve the treatment of this disease process. These new drugs, Amatadine and L-dopa, have been widely studied and tested in a number of clinical centers throughout the country. In the clinical center at the Peter Bent Brigham Hospital, the effectiveness of L-dopa in alleviating the characteristic stiffness of body muscles in patients with Parkinson's disease was demonstrated in a large number of patients. This was one of the first institutions to document the side effects of this drug and establish criteria for dosage schedules. Similar studies have been repeated and expanded upon at the clinical center at Bowman Gray School of Medicine.

Drug Abuse

Drug abuse is now accepted as one of the most profound problems facing our society today. In spite of the magnitude of this problem, and the length of time it has existed, little is known about many of the drugs which are commonly used. In the clinical center at Vanderbilt University, studies are being done to describe physiological and psychological changes as increasing doses of d-amphetamine drugs (cerebral stimulants) are administered to amphetamine dependent individuals. These studies show that amphetamines produce psychoses. Subjects experienced mild euphoria, quickly replaced by depression, followed by a prepsychotic and a definite paranoid psychosis. Physiologically, amphetamines appeared to deplete the body of naturally occuring substances and to influence blood pressures. These studies not only provide important information relating to drug abuse and dependency, but suggest the basic mechanisms associated with development of paranoid psychosis. Hopefully, information gained through this study and ones like it at other Clinical Centers may help to improve our treatment and management of drug dependent individuals.

Pulmonary Emboli

Blood clots that form in the veins and then are deposited in the arteries or the lung account for the sickness and death of many Americans each year. These so-called pulmonary emboli have been observed as one of the complications of birth control pills. An agent that can restore circulation by dissolving these clots has been a long sought after goal of many clinical investigators. Streptokinase, an enzyme produced in the laboratory by bacteria, has recently become available in sufficiently pure form to be tested on patients. At the General Clinical Research Center at Temple University and at the University of Oregon, studies are under way assessing the action of this enzyme with modern x-ray techniques. Results have been extremely promising in that pulmonary clots are found to dissolve much more rapidly in patients treated with this new drug. The studies have been extended and streptokinase is now being tested as a drug to unclot arteries of patients with severe vascular disease who otherwise may lose limbs because of inadequate blood supply.

Paget's Disease

Paget's disease, a disease that involves rapid destruction of various bones of the body, and osteoporosis, a disease which involves the depletion of bone calcium stores and is particularly common in women, are being studied at a number of clinical centers throughout the country. Both of these disease processes, if untreated, may cause severe deformity and debility in the affected individuals. Up to the present time, there has been little hope for these affected individuals and the diseases have proceeded relentlessly toward physical disability. At the clinical center at Roswell Park, studies have confirmed the efficacy of mithramycin, a new antibiotic with the unique characteristic of controlling hypercalcemia of malignant origin. Studies have indicated that control of symptoms and biochemical abnormalities of both the above diseases may be obtained by the judicious use of small doses of mithramycin.

Hypertension

If untreated or poorly controlled, high blood pressure or hypertension will lead to progressive vascular damage which, in turn, may result in premature cerebral stroke and coronary occlusion. Scientific investigation in this area is of extreme importance since close to 50 percent of the people in this country die of vascular diseases. The problems of treatment and diagnosis of various forms of hypertension are being actively studied in a number of Clinical Research Centers around the country.

In recent years, scientists have discovered the cause of several types of hypertension that had previously been classified as "essential." The adrenal gland has been associated with several types of hypertension through its overproduction of hormones which raise blood pressure. Overproduction of aldosterone by an abnormally functioning adrenal gland or adrenal tumor is

one important cause of hormone-related hypertension. This disease entity was discovered on the Clinical Research Center at the University of Michigan.

Scientists at the San Francisco General Hospital have observed that of the two pathological types of primary aldosterone overproduction--aldosterone-producing adenoma, and nodular adrenal hyperplasia--only the first is successfully managed by surgical removal of the adrenal gland. To avoid the risk of a nonproductive surgical procedure, they have embarked on a program to distinguish these two entities without resorting to surgery. Using a complex measurement of plasma renin concentration under special conditions, these investigators can successfully separate the group of patients who can expect to benefit from surgery from those who cannot.

At the University of Colorado Research Center clinical studies of a new hypertensive drug, minoxydyle, are under way. Although drugs for the treatment of high blood pressure have been available to medical practice for several decades, none of these have been entirely satisfactory in the control of arterial hypertension, particularly because of their side effects. With minoxydyle, the reduction of blood pressure is done by direct attack on constrictive blood vessels. This agent relaxes these vessels without many of the side effects attendant with other antihypertensive drugs. When carried to conclusion, these studies will define the therapeutic potential of a powerful new antihypertensive drug which may develop a new and hitherto not possible approach to therapy.

Drug-Related Research

The area of drug testing and drug development for therapeutic purposes has been of tremendous interest to clinical investigators and researchers throughout this country for many decades. The Clinical Centers have provided an ideal environment for the testing and development of several specific drugs as cited above with minoxydyle.

Another example of drug-related research is found at the Buffalo Children's Hospital Clinical Center. Researchers at this institution were responsible for delineating the pathways of salicylate metabolism. This information has aided greatly in the treatment of aspirin intoxication and poisoning, particularly in children.

Patients with peptic ulcer disease receive large amounts of antacids and antispasmodics. Because many other drugs are administered to patients who are receiving antacids, the effect of antacids on the absorption and interaction of these various drugs is very important. At the University of Kansas Medical Center, this facet of antacid therapy is being thoroughly studied in man and important information is being gained on the effect of antacids on drug absorption.

c. Community Involvement

A specific goal of the Program is to maintain ongoing interchange between clinical investigators and practicing physicians in surrounding communities. In many communities, physicians look to clinical centers as sources of important new information and techniques relating to patient care. Research seminars, conferences, ward rounds, and publications emerging from clinical centers assist the practicing physician in his awareness of new methods of diagnosis and treatment. National programs of continuing medical education depend heavily upon these centers for dissemination of new knowledge and demonstration of improved health care services for members of local medical communities.

The four examples given below of the interchange possible between centers and the local community should suffice to highlight this fact of center impact.

1. The research dietitian's role within the center at the University of Washington has recently involved the formulation of programs directed to the improvement of nutrition and dental health in the Head Start Program within the central area of Seattle, as well as providing leadership in devising a program format, materials and recipes of instruction for patients with diabetes mellitus within the Seattle community.

2. At Stanford University, a first-time concept for non-Stanford University medical students was initiated on the Clinical Center. A first-year student from another medical school was assigned a patient to "live with" for six weeks. Although supervision was under the direction of the center personnel, the student guided the patient through admitting, the business office, social work consultant, work-up, clinical investigation, etc. The relationship with the patient continued through discharge into the home social setting. The student prepared a written profile of the study subject before the investigative team, composed of faculty and nonfaculty physicians, a mathematician, nurses, dietitians, a recreational therapist, research assistants, etc. In assessing this project, University officials stated that the student seemed especially sensitive to the social needs of the patient and felt that a multi-dimensional look at the study subject was extremely helpful. This student hopes to return to Stanford next summer. Further, they stated that there was something of special value in having a student function in this manner in that "his commitment and principle thrust, therefore, was to find experiences that interested and benefited him. It was beneficial for the center and we look forward to knowing and teaching another medical student in such depth this summer."

(3) Also at Stanford University, a paper resulting from work done at the Stanford clinical center was placed in the medical library and used as the basis of a predominantly undergraduate SWOPSI (Stanford Workshop on Political and Social Issues) workshop in cardiac replacement: its projected social and cost benefit values. The SWOPSI workshop program allows undergraduates to pursue, to actually construct a "course" around their interests. The Center welcomed the SWOPSI students who included, among the undergraduates, a few law students, whose confrontations with medical students provided spirited sessions. SWOPSI courses may emerge in new ways of doing things, e.g., making system analysis procedures a method by which predisposing disease factors can be epidemiologically stated with greater accuracy.

About the SWOPSI project, the University officials stated that the "GCRC, thought of as one of the greatest resources of the medical school and always as an experimental environment, has the built-in flexibility and the staff to provide instant knowledge sharing for University students who make these welcome demands on the Medical Center."

(4) Livingston, California, a small, agricultural town several hours distant from the GCRC is the site of a Stanford University experiment in the delivery of community health care services. The sole general practitioner serving Livington opted for a residency, leaving his many patients in difficult circumstances. The Medical Center installed a full-time physician in his place, and four or five medical students live in Livingston during their months of clerkship. Nearly all GCRC investigators have taught in this small town with individual cases referred to the more controlled environment of the GCRC. The students benefit by becoming "responsible physician" to their patients, clinical investigators see more patients than they might in the Hospital, and nearby community physicians see Stanford researchers in the flesh and quite often develop relationships and referral systems helpful to each other. It was discovered, for example, that physicians embedded in small communities really thirsted for new knowledge and gladly gave up their valuable time to join investigatory rounds at the GCRC.

VI. Future Objectives and Trends

The underlying goal of the Program to provide specialized inpatient facilities designed for the conduct of excellent clinical research remains unchanged. That this Program has filled a deeply felt need within the

medical community is documented by the rapid and progressive increase in the number of Centers applied for and funded during the ten-year history of the Program. As pointed out earlier, the productivity of the Program may be documented quantitatively by the progressively increasing number of papers produced annually by all the Centers and qualitatively by the quality of the scientific journals in which they appeared. However, recent analyses of Program function coupled with increasing budgetary constraints indicate that there remain a number of mechanisms by which the quality of the science generated by this Program may be further improved.

Although Centers are currently extant in two-thirds of the teaching medical institutions in the country, a number of institutions with great potential for scientific excellence do not as yet have Centers. Among the highest priorities of the Program is the funding of high priority applications for new Centers. The Branch currently has three applications of very high priority. Between one and four additional high priority applications are anticipated to be received by the end of fiscal year 1973. Highest priority should be placed on funding of these Centers.

A large need has been documented by program staff for facilities for the conduct of ambulatory clinical research. In recognition of this need, all existing Centers have been allowed the option of modifying their current facility to enable increasing use of ambulatory patients as research subjects. A number of Centers (30)have acted on this option, and many others have indicated their interest. The use of Center facilities for such research requires some renovation of existing facilities and some redistribution of personnel allocations within the grants. In Centers where the demand for ambulatory facilities is substantial, supplemental funding will be required to develop a more elaborate facility and nursing staff.

Continued budgetary constraints have required and will continue to require reduction in the level of support in Program activities in all Centers. However, care has been taken and will continue to be taken to insure that within the confines of available funds, the Program continues to supply the best possible clinical research resources support. As the most flexible and costly element in most of the Center budgets is hospitalization costs, reduction in hospitalization awards will create pressure within an institution to utilize unfunded beds for service activities. This is particularly true in those hospitals where an acute bed shortage exists. In order to circumvent an undesirable shunting of beds from research to service use, the Program has established a discrete costing method in which in effect the entire Center area is "rented" from the institution at cost and ancillary services for patients admitted to the unit are awarded on a fee-for-service basis. This mechanism appears to have wide acceptance among hospitals and Program Directors; however, negotiation of this method of reimbursement has lagged, and another year likely will be required before the impact of this new method can be accurately assessed on a Program-wide basis.

Centers have been given an option to establish a service patient policy in which research done on patients who require hospitalization for their illness is in part reimbursed through third party mechanisms. This system has the advantage in that beds unfunded by the Program do not devolve to a purely service function but rather remain available for "research" patients at little or no cost to the Program.

As part of the continuing effort to insure quality control of projects conducted within the Centers, improved reporting procedures and program planning methods are being developed. Annual Reports from the Centers are being analyzed to determine which investigators have peer reviewed grant or contract support in addition to that available from the Clinical Research Center. Amounts and other data for such outside grant support are being determined and will be subjected to detailed analysis. The data and analysis will be used together with Committee and Council recommendations, as an improved guide in establishing the proper support level for individual Centers.

VII. Special Program Projects

During fiscal year 1971, Program staff has cooperated with Alan Landsburg Productions in the production of an hour-long television documentary entitled, "How To Stay Alive." This documentary serves the public function of informing large populations of people of the most recent scientific information on the relationship between life-style and continuing health. In recent years, the influence of such risk factors as family history, obesity, lack of exercise, blood cholesterol and triglyceride levels, hypertension, smoking, and stress on the likelihood of cardiovascular disease, myocardial infarction, and stroke have become increasingly known to the medical community but much less well known to the population at large. For the documentary, five representative American men were selected and examined by General Clinical Research Center physicians. The results of these findings were presented to the patients, and recorded in film, for the television program. In this dramatic fashion, information was presented to the American people as to how life-style is endangering the health of large numbers of American men and positive information is presented relating to how these life-styles may be altered to promote better health. Through the agency of this television documentary, the General Clinical Research Centers Program feels strongly that it is making a direct contribution to improving the health of the American people. Also, the television program can but serve to make many other contributions of this Clinical Center program better known to the American people.

A second public service activity which the Branch has undertaken within the past year has been preparation of a booklet on "Recent Clinical Research Advances in Child Growth and Development." This booklet, designed for the intelligent layman, but of sufficient sophistication to be useful to medical students and to the nonspecialist physician, undertakes to review new clinical research findings which have been derived from research in child growth and development within the past several years. The majority of the

work detailed within the booklet has resulted from efforts on General Clinical Research Centers; however, clinical research results from efforts other than on clinical research centers have been included and given prominence consistent with its importance. The booklet, when published in late summer of 1971, should serve again to underline the importance of clinical research in one circumscribed area and to demonstrate the degree to which work supported by the General Clinical Research Centers program is involved in that effort.

Fiscal Year 1971
ANNUAL REPORT
Animal Resources Branch
Division of Research Resources

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Fiscal Year 1971
Annual Report
Animal Resources Branch
Division of Research Resources

INTRODUCTION

The overall objective of the Animal Resources Branch is to support activities that provide, or enable biomedical scientists to effectively use animals to develop knowledge for the prevention and control of disease in man. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The Branch objectives are accomplished through a Primate Research Centers Program and a Laboratory Animal Medicine and Vivarial Sciences Program.

I. PROGRAM AREAS

PRIMATE RESEARCH CENTERS PROGRAM

The Primate Research Centers, established and operated by Federal grant funds, provide an unique research environment where biomedical research in a number of important areas is being conducted. The programs of the seven Centers are directed toward problems particularly relevant to diseases of man. During this year valuable contributions were made in the areas of infectious diseases, reproductive biology and population control, mental health and mental retardation, nutrition, and cardiovascular diseases.

This year, salary support was provided for 722 employees, including 118 doctoral-level scientists and 604 technical and administrative support personnel. A total of 274 collaborative scientists from a number of domestic and foreign institutions utilized these specialized facilities for varying periods of time. Also, the research facilities of the seven Centers were utilized by a total of 124 graduate students for part or all of their thesis research. In addition to the research support provided by this Program, the Center staff engaged in 90 other federally supported research projects totaling $3.2 million. Collaborative scientists utilized these facilities to support part or all of numerous research projects totaling $2.0 million. During this year the core staff published a total of 591 scientific publications and 21 books.

The DHEW Audit Agency conducted extensive audit reviews of the three centers not previously audited by the General Accounting Office. In general, the reviews were satisfactory and the majority of the recommended internal administrative changes have already been implemented.

The Program continued the sponsorship of workshops and conferences on subjects of current interest and importance to scientists using nonhuman primates. Two workshops were conducted; namely, a) Communications/Information/Public Relations and b) Nonhuman Primate Virology. The proceedings of the latter will be published in Laboratory Animal Science as a special supplement.

In order to improve the overall Program, extensive reviews and evaluations were conducted by the Primate Research Centers Advisory Committee, by the National Advisory Research Resources Council, and by the staff. Certain areas requiring more in-depth studies were identified and a special planning committee composed of consultants and staff was established. Preliminary recommendations regarding the future role of this Program have been developed and will be considered by the advisory bodies and by various NIH administrative echelons during the coming year.

Research activites at the various Centers are as follows:

Oregon Primate Research Center

The primary mission of the Oregon Center is reproductive biology and population control; some 15 investigators are currently conducting research in this area. In addition, studies are being conducted in immunology, cardiovascular diseases, nutrition, and cutaneous biology. The following are examples of research at the Center:

1. The Effects of Early Malnutrition on the Nervous System and Behavior of Primates

New research recently initiated is designed to determine how protein deprivation during the critical early stages of growth affects the development of the central nervous system and the psychological behavior of monkeys. Studies on infant monkeys maintained on a low-protein diet for the first year of life suggest that protein-deprived infant monkeys do not compete favorably with their well-nourished peers. Malnourished monkeys are demonstrably less agressive and deficient in play. This research will enable the scientists to relate the effects of early nutritional deprivation on behavior to specific chemical, biochemical, and structural changes in the growing brain and should lead to an understanding of how malnutrition affects these changes.

2. Hair Follicle Metabolism

It has been shown for the first time that human hair follicles contain the sex hormone-sensitive enzyme, adenyl cyclase. Also, hair follicles convert testosterone to the dihydro form. Adenyl cyclase is activated by the female hormone estrone and inhibited by dihydrotestosterone. This marked enzymatic inhibition suggests dihydrotestosterone plays a physiological role as a tissue-active androgen in the initial development of pattern baldness.

3. Progress in Tissue Transplantation

A method has been developed for purifying an antilymphocyte antibody that provides a 20-to-100 fold increase in leucoagglutin activity. A purified serum delays the rejection of skin grafts in rhesus monkeys by more than 25 days beyond the normal 10 days. Current studies are seeking to determine the mechanism of

preventing rejection and to evaluate the application of this antibody to human skin and kidney grafts.

Delta Primate Research Center

The primary research orientation of the Delta Center is in the area of infectious diseases with other programs in reproductive biology, behavior, and environmental health. Specific research examples are as follows:

1. Hookworm Disease and Control of Anemia

The hookworm still remains an important cause of morbidity in the tropics and is considered one of the important retarding influences on community development. Many aspects of hookworm disease have been difficult to study in the laboratory due to the lack of a good experimental system. Recent studies have shown that certain primates can be infected with the human hookworm and that the parasite behaves in primates essentially as it does in man. Therefore, laboratory studies using monkeys and apes as experimental models will assist in developing a better understanding of hookworm disease, and the significance of the hookworm in the production of anemia.

2. Techniques Applicable to Population Control

Three interesting studies in reproductive biology relating to population control were conducted at this Center: a) the administration of low doses of progesterone over a short interval into female rhesus monkeys will inhibit ovulation by preventing the release of pituitary hormone; b) the administration of testicular homogenate into mature male chimpanzees and rhesus monkeys results in testicular degeneration as a result of the high antibody titres produced against testicular antigens; and c) impregnation of silastic intrauterine devices with progestin will significantly reduce the rate of expulsion when these devices are placed into the uterine cavity of female animals.

Yerkes Primate Research Center

The Yerkes Center is largely devoted to biomedical studies using the greater apes, including the chimpanzee, gorilla, and orangutan. Their research program is primarily in neural and behavioral sciences with additional programs in degenerative diseases and immunology. Research examples are as follows:

1. Cross-Modal Transfer of Information

It has been demonstrated that apes have the property of cross-modal transfer of information. In other words, if they are shown a geometrical shape or even a photograph of one, they can subsequently select the correct shape by touch only. Previously, scientists have claimed that only man has this ability of perceptual integration, but the fact that apes can perform this task, and that

no monkey can, shows that the ape's brain is more like man's than was realized before. These studies should be interesting to diagnosticians who deal with aphasias, agnosias, and apraxias resulting from head injuries, strokes, and similar disorders.

2. First Animal Model for Study of Human Alcoholism

For the first time, an animal model of alcohol induced physical dependence has been experimentally produced in man's closest relative--the chimpanzee. Preliminary results indicate that 8-10 consecutive weeks of relatively high alcohol consumption can produce mild to severe withdrawal symptoms when alcohol intake is abruptly terminated. Work during the coming year will be devoted to determining what factors are critical in producing and treating this condition which may affect an estimated 3 million persons in the U.S. each year.

Washington Primate Research Center

The Washington Center is primarily interested in neurophysiology relating to cardiovascular functions, with additional programs in oral-facial growth and development, metabolism, and behavioral research. The following results are being produced by this research program:

1. Cardiovascular Response to Environmental Conditions

In order to examine the relationship between somatic behavior and cardiovascular responses across the full physiological range, a complex environmental control situation has been developed. Monkeys maintained in restraint chairs have been instrumented with blood flow and arterial blood pressure devices. This procedure has been used to obtain data on: a) normal individual variability in response to each stimulus condition; b) influence of a tranquilizer; and c) hypothalamic and prefrontal control of various cardiovascular responses. This technique allows one to accurately assess the relative contribution of environmental factors as opposed to neural factors in the generation of a cardiovascular response.

2. Collaborative Research Efforts

This Center supports a very active collaborative research program involving some 30 investigators from the University of Washington and nearby institutions. A wide variety of research activities are being conducted in the Center that could not be conducted elsewhere in the University as the facilities and expertise would not be available. These include programs in auditory physiology, visual systems, orthodontic research and dental physiology, behavior, histocompatibility and organ transplantation, metabolism of Vitamin D3, evaluation of antithrombotic agents, temperature regulations, and a number of other projects.

Wisconsin Primate Research Center

This Center is working in two broad areas; namely, neural and behavioral sciences and reproductive endocrinology. The following are examples of their research program:

1. Research Relating to Population Control

Studies were conducted to determine the physiologic factors which regulate the corpus luteum during the preimplantation and early postimplantation stages of pregnancy in monkeys. Current evidence indicates that in the monkey, like the human, the ovaries are necessary for only a limited period of time during pregnancy. Ovariectomy of the pregnant rhesus monkey during the early postimplantation stage does not interfere with the excretion of chorionic gonadotropin, pregnancy or the delivery of normal infants. Hypophysectomy causes a marked decrease in excretion of chorionic gonadotropin and termination of pregnancy. This suggests that in intact pregnant monkeys pipuitary and/or non-pituitary hormones are necessary for the maintenance of the corpus luteum, the secretion of chorionic gonadotropin and pregnancy. These studies should provide meaningful information in identifying the critical phases during which early pregnancy can be terminated and the basis for developing more effective contraceptive and abortifacient agents.

2. Induction and Treatment of Depression in Infant Monkeys

A program to produce profound and persistent depression in young rhesus monkeys is underway. Two techniques have been developed involving the complete separation of infant monkeys from other animals. Both of these behavioral techniques produce stable depressive states which persist for more than one year. The production of stable depressive states in monkeys makes a meaningful search for associated biochemical variables an experimental possibility, regardless of whether these biochemical variables are the cause or the consequence of induced depression. Certain pharmacological agents thought to predispose the human to depression are being administered to monkey subjects. The effects of these drugs will be measured and hopefully these studies will lead to a better understanding of depression in man.

New England Primate Research Center

The research program of this Center is focused on infectious diseases, pathology, and the support of collaborative research. Research examples are as follows:

1. Spontaneous Abortion in Monkeys

A series of spontaneous abortions occurring in wild-caught rhesus monkeys have been studied. It has been determined that the abortions or stillbirths result from severe thrombosis of the placental blood vessels which result in infarction and death of the placenta. Preliminary evidence seems to indicate that placenta thrombosis and infarction may be related to a virus infection which pregnant monkeys contact from man shortly after capture.

2. Leukemia in Monkeys Caused by Herpesvirus Saimiri

Studies have demonstrated for the first time that a Herpesvirus induces leukemia in monkeys. This finding is of particular significance in that it provides a primate model system in which anti-cancer chemotheraputic agents can be tested as a means of preventing leukemia. Recent circumstantial evidence has led to speculation that Herpesvirus may be a cause of cancer in man. The demonstration of this in other primates such as the monkey adds sound evidence in support of this hypothesis.

National Center for Primate Biology

The research mission of this Center currently is quite different than that of the other six Centers in that it is devoted primarily to studies on primate biology. Programs on caging, disease control, breeding, and the establishment of biological profiles for several important primate species are underway. This Center also participates in an active collaborative program.

1. Development of Outdoor Caging Facilities

Emphasis is being placed on the development of outdoor caging facilities to cheaply and efficiently house the large number of nonhuman primates required in biomedical research programs. Such efforts are critical, not only because of the increasing difficulty in obtaining these animals from their natural habitat, but the demand for animals of known parentage and with documented medical histories is increasing rapidly. A wide variety of outdoor caging has been developed and is being evaluated. Preliminary studies indicate that primates can be maintained in outdoor cages in the central California area. Animals maintained outdoors are healthier, more active, display a more normal social behavior and breed better than animals housed indoors. The cost of maintaining animals outdoors is substantially less than that for indoor housing.

2. Physiological Consequences of Chronic Exposure to Environmental Toxicants

Studies on the physiological consequences of long-term exposure to low levels of toxicants are being conducted by one of the collaborative scientists. The purpose of these studies is to develop an understanding of the physiological nature of subclinical body burdens of specific toxicants, and to develop rationale for setting safe limits on exposure levels. The toxicant DDT is being employed to determine the neurophysiological effects of chlorinated hydrocarbon insecticides in the rhesus monkey.

LABORATORY ANIMAL MEDICINE AND VIVARIAL SCIENCES PROGRAM

The objective of the Laboratory Animal Medicine and Vivarial Sciences Program is to significantly improve the capability of institutional animal resources to serve medical research and education programs. This mission has been accomplished through grants for support of disease diagnosis and control, research related to improving animal health and care, special animal colonies that are of unusual nature and special value for certain types of research, studies directed to enhancing the usefulness of animal models for research, general improvement of management and accommodations for institutional animal resources, and post doctoral and special research training. The Program received appropriations of $4.952 million in Fiscal Year 1971 and provided support to 66 discrete animal resource projects, 9 training programs and 12 fellowships.

1. Resource Projects

An important facet of research utilizing experimental animals is assurance that the animals are in an optimal state of health. This basic goal is dependent upon the ability to recognize and evaluate intercurrent laboratory animal diseases. Diagnostic laboratories were supported at 19 institutions where they made basic contributions to an investment of over $80 million in research projects utilizing animals. These resource projects served both to provide basic support for the animal health program and to seek new information on the etiology and nature of disease processes. New animal models of human disease have also been defined. Examples of these activities include the diagnosis and control of bacterial pneumonia in monkeys used for malaria studies, control of an outbreak of diploccus pneumonia that had resulted in the death of 250 guinea pigs used on a nutritional research project, the diagnosis of diabetes in the South African hamster, thus identifying a valuable model to study this disease, and the discovery of a Siamese cat family with beta galactosidase deficiency which shows extraordinary potential as an animal model for neuronal GM-1 gangliosidosis, an important human disease. One diagnostic laboratory has made a special effort to study iatrogenic lesions (experimentor induced disease) and has thus significantly reduced such complications by suggesting improved techniques to investigators.

Several projects supported by the Animal Resources Branch have made significant contributions to an improved understanding of chronic murine pneumonia, an important and devastating disease of laboratory rats. Animal Resources Branch supported studies conducted at the University of Alabama Medical Center and at Michigan State University have contributed a new insight into the pathogenesis of the condition and have helped confirm Mycoplasma pulmonis as the principal etiologic agent.

An important area of the Program relates to the support of a number of special animal colonies which have proven to be extremely valuable in human health-related research. In most cases, animals from these colonies are available to qualified researchers from other institutions upon request. A case in point is the provision of approximately 40 laboratory-conditioned hemophilic beagles dogs (heterozygous and homozygous for factor VIII deficiency) to 10 investigators (representing 5 research institutions) from a colony at Oklahoma State University. Examples of other special animal colonies which have been extremely useful in research activities include genetically epileptic rabbits, obesity-prone rats, inbred guinea pigs used in immunology studies, germfree rats and mice used in air pollution research, and germfree beagle dogs used in a variety of research projects, including hemorrhagic pancreatitis, tumor growth, hemorrhagic shock, and nutritional studies.

Nine institutional primate resources have been supported by the Animal Resources Branch. Nonhuman primates have been maintained in specialized facilities under optimal conditions of animal care and medical supervision where they were made available for multidisciplinary types of biomedical research. These resource grants have also contributed to the economy of research using primates by providing a framework for the multiple or sequential use of these animals. These resources were utilized in over 140 discrete research projects, including the areas of reproductive physiology and fetal development, neonatal asphyxia, hepatitis, and organ transplantation. Support for the research which utilizes these institutional primate resources approximated over $7 million.

The Program has continued to support studies for the establishment of anatomic, biochemical, and physiological baselines on colonies of animal species which have exhibited the potential of developing into valuable research and educational resources. Data of this nature amassed at the University of Missouri has significantly advanced the use of miniature swine as a research model in a number of investigative areas, including alcoholism, nutrition, microbiology, dentistry, reproductive biology, lipid metabolism, genetics, development of myelin, physiology, and social behavior. This type of resource support has advanced knowledge to the stage where several grant applications for specific research projects utilizing miniature swine have evolved.

Squirrel monkeys (Saimiri sciureus) have been found to be excellent animal models for studies of atherosclerosis at the Bowman Gray School of Medicine. Animals were trained to "jog" for two hours each day and are currently being evaluated to determine the effect of such exercise on serum lipid levels, blood pressure, electrocardiograms, and the extent and severity of coronary artery disease. A particularly exciting recent development is the use of genetically-defined squirrel monkeys to determine the genetic control of serum cholesterol. Studies to date with these animals indicate that more than 90 percent of the total variability in serum cholesterol in the progeny can be attributed to genetic factors. Apparently, the genetic control of serum lipids in squirrel monkeys is nearly identical to that of humans. Thus, we have an animal model of hyperlipoprotinemia, a condition that has recently received great attention by the National Heart and Lung Institute. If a single major gene is involved, it may be possible to identify "high risk" individuals early in life. The animal model will also be useful in the development of drugs to control hyperlipoproteinemia.

Adaptation and characterization studies on new species of arctic wild rodents (e.g., lemmings) at the University of Alaska have enhanced their usefulness in studies of physiological adaptation, hibernation, energy metabolism, cold acclimitization, and middle ear infections. Support has been provided for a project at the Gulf South Research Institute to develop the armadillo as a model for use in several types of research with particular emphasis on developmental biology. As a result of initial work on the Animal Resources Branch-supported project, a National Communicable Disease Center grant has been awarded to develop the armadillo for leprosy studies. The low body temperature of the armadillo (32° to 35°C.) makes it suitable for leprosy research because the causative organism proliferates most readily at these temperatures.

Another example of an interesting and highly significant animal model development, which was accomplished at the Washington State University animal resource, concerned the induction of teratogenic effects on salmon fry by treatment with tetracycline in various doses. The specific anomolies observed in the salmon fry are the same as those induced in mammals by high doses of tetracycline. This inexpensive animal testing model represents an important advancement in screening for potential teratogenic effects of numerous drugs and other chemical compounds.

Institutional animal resource improvement projects have been an important program activity. At the present time, 14 institutions are being assisted in their effort to develop strong central programs to support their biomedical research program. Grants for this purpose provide funds for the purchase of special equipment such as cages, cagewashers, etc.; for minor renovations to improve facilities; for support of key professional and supervisory personnel; and for support of clinical laboratories to improve health programs. The Animal Welfare Act of 1970 is expected to

be the basis for an increased demand to upgrade institutional animal facilities and equipment. However, unless additional funds for this purpose are added to the Animal Resources Branch budget, we will not be in a position to support any expansion in this area.

The Animal Resources Branch Program also supported several reference center and information projects. Examples of these are:

a. A simian virus reference laboratory at the Southwest Foundation for Research and Education at San Antonio, Texas. This is the only "all inclusive" primate virus laboratory in the world, and now has a working repository of over 60 virus reference reagents and reference antiserums. Ongoing activities of the project are designed to give information regarding the immune status of subhuman primates and the possible cause of outbreaks of overt diseases. Institutions throughout the country have taken advantage of this program. Service functions for outside investigators are of two basic types:

(1) Screening sera for the presence of antibodies against a battery of simian and human viral antigens; and

(2) attempted isolation and identification of viruses from a variety of specimens from sick or apparently healthy animals.

Serum surveys have provided a great deal of information pertaining to infections of specific simians, geographic distribution, and effect of captivity on the various primates at different laboratories. For example, a recent study compared the antibody status of different new and old world monkeys maintained by Dr. Cooper (NCI contractor) at the San Diego Zoo. An ongoing survey is screening primates for evidence of infection with hepatitis (Australian antigen and antibody) and EBV (Burkitt's lymphoma).

b. A small project aimed at developing a registry listing various specialized lines, special stocks containing mutant genes and rare breeds and varieties of domestic chickens is being supported at the University of Connecticut. The initial section on specialized lines (98 lines are listed in the registry) is now completed, and work on the section concerning mutant genes is in progress. The registry will contain information describing the various conditions, appropriate literature references, where the stocks are located, and their availability. This project will be of great value to scientists by enabling them to identify and locate useful avian models for their research. Examples of useful avian models include diabetes insipidus, renal riboflavinuria, hereditary autoimmune thyroiditis, and muscular dystrophy.

2. Training Grants

Training grants are awarded to academic institutions to provide postdoctoral training in laboratory animal medicine. The training is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team. Twenty-six trainees are currently enrolled in nine training programs. The usual period is two to three years.

Forty-six trainees have completed training since the inception of training grants in laboratory animal medicine. Twenty-six of these are employed by medical schools and fifteen by other academic, research, or governmental organizations. The majority (27) are functioning as directors or staff members of a vivarium, sixteen are engaged in research or are obtaining additional training, and three are engaged in public health and other activities. Although the number of graduates is relatively small, they have filled vitally needed leadership roles in the field of laboratory animal medicine. The rapid progress in developing strong central animal resource programs and in expanding the "state of the art" may be attributed in large part to the influence of these highly trained individuals. A further accomplishment realized from this Program is that it is serving as a catalyst to develop special courses at the undergraduate level in schools of veterinary medicine.

3. Fellowships

The Laboratory Animal Science Fellowship Program is being supported by an appropriation of $126,000 for Fiscal Year 1971. Twelve fellows are being funded during Fiscal Year 1971. This fellowship program includes both postdoctoral and special fellowships available to qualified individuals who hold the D.V.M., M.D., Ph.D., or similar degree. Candidates can engage in indepth studies in a discipline or specialty such as surgery, anesthesiology, pathology, virology, nutrition, or immunology through which they can contribute to research animal resources. This Program is designed to produce the highly specialized person who can make significant contributions to our knowledge regarding laboratory animals.

Table 1. Primate Center Program, FY 1971

pe of Application	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
.....	-	--	-	--	-	--
ewal.....	5	8,777,428	5	7,330,989	5	8,243,830
plemental.....	1	19,629	1	19,629	1	19,629
tinuation.....	2	2,906,453	2	2,860,895	2	2,236,541
als.....	8	11,703,510*	8	10,211,513*	8	10,500,000**

Direct Costs Only
Includes Indirect Costs

Table 2. Animal Resource Projects, FY 1971

pe of Application	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
.....	28	1,484,905	13	609,341	3	233,224
ewal.....	13	1,243,325	12	802,879	10	795,297
plemental.....	4	30,606	4	30,606	4	33,985
tinuation.....	53	5,020,376	53	3,266,450	53	3,411,494
als.....	98	7,779,212*	82	4,709,276*	70	4,474,000**

Direct Costs Only
Includes Indirect Costs

Table 3. Training Grants in Laboratory Animal Medicine, FY 1971

Type of Application	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amour Funde
New.....	-	--	-	--	-	--
Renewal.....	-	--	-	--	-	--
Supplemental.....	-	--	-	--	-	--
Continuation.....	9	678,089	9	596,705	9	352,0
Totals.....	9	678,089*	9	596,705*	9	352,0

* Direct Costs Only
** Includes Indirect Costs

Table 4. Fellowships In Laboratory Animal Science, FY 1971

Type of Application	Number Received	Number Approved	Number Funded	Amount Funded
Type.....	6	4	4	23,617
Renewal.....	1	1	1	12,875
Continuation.....	7	7	7	89,508
Totals.....	14	12	12	126,000

II. ADMINISTRATION

The Animal Welfare Act of 1970 (P.L. 91-579) became law in December 1970. The purpose of the Act is to prevent the theft of animals and to provide for the humane care of animals used in research, exhibition, or intended for sale as pets. The law is administered by the Department of Agriculture, but it will have its principal impact on research and educational institutions upon which the National Institutes of Health depends for the implementation of its programs. Therefore, the Animal Resources Branch was requested to develop a report on The Probable Impact of the Animal Welfare Act of 1970 on the Biomedical Research Community with Special Reference to NIH. The report concluded that research institutions must make at least a minimal adequate response to the requirements of the Act. Major expenditures would be required for alterations and renovations and modern, appropriately-sized cages and other equipment. Such improvements will benefit research through the improved care of animals. The report further concluded that a reasonable program to assist institutions to comply with the Animal Welfare Act could be spread over the Fiscal Years 1973 to 1977 and that approximately $5 million annually should be added to the Animal Resources Branch budget for this purpose.

A related animal welfare activity for this past year has been to work with appropriate policy-making and review groups to develop a NIH policy for the care and treatment of animals used in its grant-supported programs. This policy statement is currently in the final stages of review.

The Animal Resources Branch prepared a comprehensive Program Plan during the past year. Program plans for the Primate Centers are to identify a number of important research areas where the nonhuman primate is the experimental animal of choice and then to build programs of scientific excellence in these research areas. Research areas tentatively selected for development include reproductive biology and population control, neuro and behavioral sciences, nutrition, infectious diseases, and environmental health sciences. A determination will be made of the research areas best suited for development in each Center. A given Center will develop only one to three closely related research areas and thus will be able to build indepth competence in its scientific area. However, each Center will develop different research areas; thus, the national program will be balanced and resources will be available for research in most scientific fields where the nonhuman primate is used. The Primate Centers will do research in primate biology and medicine as required to support the specific mission of each Primate Center and further enhance the utility of nonhuman primates as research resources. The Primate Centers will also continue to serve as resources to be utilized by collaborating and visiting scientists.

Program plans for the Laboratory Animal Medicine and Vivarial Sciences Program include development of new knowledge about laboratory animal diseases and environmental requirements; development of new animal models and enhancement of the utility of available animal models in response to changing research requirements; assistance to institutions to apply the best available technology and management to their animal resource programs; and support of specific national animal resource reference centers. Program plans are to significantly increase emphasis on those projects that advance animal resources through production of new knowledge or through development of new technology. This is

contrasted with a decreased emphasis on projects that provide support for established and ongoing animal resources. To merit support, animal resource projects must have the potential for broad utility in support of NIH programs.

Fiscal Year 1971
ANNUAL REPORT
General Research Support Branch
Division of Research Resources

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Fiscal Year 1971
Annual Report
General Research Support Branch
Division of Research Resources

Introduction

The General Research Support Branch (GRSB) is charged with the responsibility of administering programs designed to assist institutions in the development of their scientific research capabilities so that they may become or remain effective partners of the Federal Government in the pursuit of mutually important biomedical research and research training objectives. Because the success of the National Institutes of Health (NIH) research and research training programs depends heavily upon the nation's academic and other research institutions, it is in the NIH's best interests that these institutions be encouraged to achieve and maintain the highest level of excellence in health-related research and research training programs. Because the goals of the GRSB's programs coincide with the general well being and effectiveness of the nation's health research institutions, pursuit of these goals results in a vigorous and fruitful national health research and training capability which should undergird the eventual accomplishment of fundamental as well as targeted research.

The nature of the GRSB's programs are such that they provide maximum flexibility to the grantee institution and restore as much as possible the grantee's responsibility and authority over the emphasis, direction, content, and quality of the entire research effort of the institution. The provision of flexible fluid funds for the general support of research and research training therefore complements the research project grant system and should enable an institution to participate more effectively in the pursuit of national research goals.

GENERAL RESEARCH SUPPORT GRANT PROGRAM

The most important features of the program can be summarized as (1) a quick and effective mechanism for institutions to respond to their peculiar research problems, (2) a flexibility which enables the individual grantee to respond to those individual problems, (3) the delegation of the authority and responsibility for the spending of these funds to the institution, and (4) an extremely broad yet realistic interpretation of what may be appropriately supported by the institution as health-related research or research training. Selected examples of how grantee institutions use their funds to pursue the various objectives will be found in Appendix A.

Fiscal Considerations

General Research Support Grants (GRSG) are made annually for the period from January 1 through December 31. Awards are computed by a formula which, in addition to other considerations, is based on the amount of appropriate NIH and NIMH research project grants awarded to the institution within the latest completed 12-month period, July 1 through June 30, inclusive.

Table I summarizes the level of funding and the number of grantees supported in this program since 1962. The table reveals that the funding of this program reached its zenith in 1968 and 1969. Only time will tell whether the nadir was reached in 1971. On the basis of the FY 1972 President's Budget, funding support will probably decline further.

Program Evaluation

The GRSB staff attempts an annual evaluation of the program based on information gained from Annual Narrative Progress and Expenditure Reports as well as the collection of research highlights submitted by institutions each year.

Some idea of the effectiveness of the GRSG funds may be obtained by reviewing the examples, cited in Appendix A, of representative accomplishments recently reported by grantees. The examples not only convey an impression of the breadth and diversity, as well as the qualities, of activities undertaken with GRSG funds, but also demonstrate how GRSG supported research is in areas of interest and benefit to all the institutes of the NIH. This in itself is a testimonial to the relevance of the work in terms of national problems and priorities.

Administrative

Although no substantive changes are anticipated in the administration of the GRSG program at this time, several minor developments should be completed within the coming year. (1) Federal regulations governing the administration of the General Research Support Grant and Biomedical Sciences Support Grant programs should be finalized and published in the spring of 1971. (2) A study concerning the origins, uses, and values of the ability of grantees to carry over funds from one grant year into another should be completed by the summer of 1971. The final results of this study could lead to recommended changes in the management of carried over funds. (3) Based on preliminary findings of this study and the need for more complete program information, revisions of the format and information requirements of the Annual Report of Expenditures and the Annual Narrative Progress Report are being proposed. These new reports will be forwarded through appropriate channels during the spring of 1971. The purpose of these revisions is to obtain more definitive data regarding the amounts of the carried over funds that are (1) obligated and (2) internally committed. (4) In keeping with the proposed change in NIH policy regarding allowances for "alterations and renovations" (A&R), the GRSB is also proposing an increased allowance for this type of expenditure.

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM

As pointed out earlier in this report, formula grant programs providing general support for research and research training activities of institutions began with the General Research Support Grant program in 1962. A

year later this program was broadened to include types of health professional schools not included in the original program as well as hospitals, local and state health and mental health departments, and non-academic health research organizations. In 1965 recognition was paid to the fact that approximately 20 percent of the NIH and NIMH research activity is conducted in non-health professional components of academic institutions. In order to extend general flexible support for research to these institutions, the Biomedical Sciences Support Grant (BSSG) program was instituted and made its first awards in 1966. The purposes, aims, and features of this program are essentially identical to those of the GRSG program. Selected examples of how these grantee institutions pursued BSSG program objectives are presented in Appendix B.

Fiscal Considerations

As with General Research Support Grants, Biomedical Sciences Support Grants are made annually (for the period from June 1 through May 31, inclusive) and awards are computed in relation to a formula which takes into consideration the amount of appropriate NIH and NIMH research project grants awarded to that institution within the latest completed federal fiscal year.

Table II summarizes the funding levels and the number of grantees supported in this program since 1966. It can be seen by comparing this table with Table I that the BSSG program has been subject to the same general fluctuations as the GRSG program.

Program Evaluation

Annual evaluations are made by the GRSB staff on the basis of grantee reports and research highlights. It is the GRSB's opinion that most, if not all, of the findings resulting from the 5-year GRSG evaluation study of 1969 are applicable to the BSSG program. This is because of the great similarity of objectives, policies, and operations of the two programs.

HEALTH SCIENCES ADVANCEMENT AWARD PROGRAM

In 1966 the Health Sciences Advancement Award (HSAA) program was inaugurated in an attempt to expand the national capability for research in the health sciences by increasing the number of distinguished biomedical research and research training institutions within the nation. The purpose of the program is to assist academic institutions to strengthen significantly their activities in health sciences by (1) supporting the advancement of new and existing health and health research training endeavors where an appropriate institutional base for such advancement exists, and (2) encouraging the development of health science activities in institutions that presently possess considerable strength in related fields of science. The HSAA program differs from the two formula grant programs in that it provides funds annually to a grantee usually for a project period of five years.

In addition, awards are competitive and each applicant institution must identify and describe in adequate detail a unifying research theme or focus within the specific institutional research proposal for which funds are requested.

Fiscal Considerations

No new awards were made in 1971, but all existing obligations were being met to the extent permitted by available funds.

Program Evaluation

The HSAA program is now in its fifth year and several of the early grantees have had the award long enough to achieve identifiable progress.

The HSAA program at the University of Virginia Medical School has provided the funds to rebuild or strengthen five basic science departments and to increase the research and training productivity of these departments. In addition to providing actual support the award has proven to be a stimulus to the State to provide increased funding. A new building of approximately 240,000 square feet to house the Basic Science Departments is scheduled for occupancy in September 1971.

The HSAA at Cornell University came at a time when the University had secured additional state and private funds to form the new Division of Biological Sciences. This combination of support was used to bring together, in the new Division, faculty who previously were scattered through numerous departments of several colleges. It was possible to appoint some new faculty members because the HSAA was available to support their salaries and to provide them with laboratory space and equipment. As a result, Cornell is becoming an institution that is eminent in the health-related sciences such as neurobiology and behavior.

The University of California at Davis, a more recent HSAA grantee, has moved vigorously in its program in comparative medicine which now involves more than 60 professional scientists from five schools and colleges of the University. The HSAA is making possible the interdisciplinary utilization of the unusual animal facilities available at Davis and more than 10 species are being investigated for comparative purposes with the ultimate objective of more accurate extrapolation to the understanding of human disease.

Dr. W. L. Pak and his associates in the HSAA Neurobiology program at Purdue University have made a successful beginning in "dissecting" the visual process genetically. The idea behind the program is to induce defects in the genes

controlling the separate single steps of the visual pathway in the fruitfly, and to study these mutants both electrophysiologically and structurally. Five mutants have been found to display abnormal electroretinograms, a diagnostic test for determining whether the retina is capable of performing the early steps in the conversion of light to electric impulses that can be integrated into visual experience. Three of these mutants are especially interesting, since they possess structurally normal eyes and retinas, yet are incapable of "seeing" as determined by behavioral as well as electrophysiological tests. Thus, an alteration in the structure of a significant protein must prevent some critical very early step in the visual process which renders the organism blind. By isolating and studying other visual or behavioral mutants these investigators hope to dissect visual and behavioral processes in the manner that has been found to be successful in learning about metabolic pathways. This is an elegant application of molecular genetics to the study of such complex phenomena as sensory processes and behavior.

The HSAA program at Rice University supports the strengthening of the biological sciences to balance the already excellent physical sciences and engineering programs. In the bioengineering component of the HSAA program, collaborative research with faculty members of the Baylor University College of Medicine have resulted in improved understanding of the mechanical properties of collagen and elastin from ligaments and arteries under continuous and pulsating stress. The stress-produced deformation has been examined both by physical and histological techniques. The Rice HSAA program has also been responsible for the establishment of a Department of Biochemistry and the attraction of a highly qualified head for it.

Recent research on behavioral neuropharmacology in the HSAA program at the University of Kansas has established that reproducible behavior patterns occur in free-moving rats. These patterns are modified in specific measurable ways by administered drugs such as amphetamine, chlorpromazine, and morphine. By computer analysis of the established patterns, as recorded by time-lapse photography of normal rats and rats on drug regimens with and without specific brain lesions, the Kansas researchers are determining the interrelationships between specific drugs and altered behavior in rats under controlled conditions of interest.

TABLE I

Number of Grantees and Funds Available for the GRSG Program
FY 1962-1971

Type of Grantee Institution	Number of Grantee Institutions									
	FY 1962	FY 1963	FY 1964	FY 1965	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971
Medicine	87	87	87	89	89	90	95	99	100	100
Dentistry	49	49	49	49	49	49	49	49	49	33
Osteopathy	5	5	5	5	5	5	5	5	5	0
Public Health	12	12	12	12	12	12	12	12	12	12
Pharmacy	-	4	5	5	5	9	10	12	15	15
Veterinary Medicine	-	9	10	11	9	13	15	17	17	17
Nursing	-	0	0	0	0	0	0	0	0	2
Hospitals	-	51	49	55	51	64	71	75	79	76
Health Departments	-	4	3	3	3	3	3	3	3	2
Research Institutes	-	43	42	44	41	49	51	58	64	69
Total Number of Grants	153	264	262	273	264	294	311	330	344	326
Total Funds Awarded (in millions)	$20.0	$29.9	$34.9	$43.8	$39.1	$41.7	$48.2	$48.2	$45.8	$43.4

TABLE II

Number of Grantees and Funds Available for the BSSG Program
FY 1966-1971

	1966	1967	1968	1969	1970	1971
Total Number of Grants	91	93	102	110	113	112
Total Funds Awarded (in millions)	$5.000	$5.990	$7.500	$7.500	$7.125	$6.777

EXAMPLES OF REPRESENTATIVE ACCOMPLISHMENTS SUPPORTED BY GRSG FUNDS

1. William Oppenheim's report on "Neuro depressant and local anesthetic activity of the quaternary ammonium salt, methyllidocaine chloride," was done in the Department of Pharmacology, Georgetown University School of Medicine while on a GRS student research fellowship. He received the Borden Award for this work at the time of his graduation in June 1970.

2. Investigators on the Clinical Metabolic Research Unit of the Jewish Hospital and Medical Center of Brooklyn, while studying a patient with an unusual form of hypoglycemia, were able to document conclusively the first case ever of hypoglycemia due to a deficiency of the pancreatic hormone glucagon.

3. Beth Israel Hospital in Boston developed a program of more sophisticated methods of monitoring both the mother and the fetus during labor. Because of this more refined monitoring system some women who might otherwise have been subjected to the surgeon's knife have been permitted to go through labor and deliver a normal child. Other women, having normal labor by older and cruder criteria, have been found by the electronic methodology of this technique to have fetuses in serious physiological distress. In those instances, surgical intervention managed to salvage infants who might otherwise have been burdened with serious neurological damage throughout their lives.

4. Using General Research Support Grant funds, the Institute for Medical Research in Camden, New Jersey, succeeded in determining the exact morphology of the virus that causes breast cancer in mice, and found that this morphology is different from any other known virus. This observation permits identification of this virus on sight. A parallel finding made during the year was that some specimens of human milk contain a virus morphologically identical with the mouse mammary tumor virus. It was also found that pregnant mice injected with the mammary tumor virus remained free of the tumor whereas virgin mice injected with the same virus were infected. These findings were interpreted as offering a potential method of immunization against breast cancer in mice. The experimental mouse model and its close similarity to the human disease, plus the development of new research techniques within recent months, hold great promise for rapid advances in this field.

5. GRSG played an important role in the organization and development of the Division of Environmental Medicine in the Department of Community Medicine of the Mount Sinai School of Medicine. This laboratory, under the direction of Dr. Irving J. Selikoff, has become a major national resource for air pollution studies. The importance of the research program of this Division has been recognized by receiving five research grants from the Public Health Service for a total of over $2 million.

6. St. Jude's Children's Research Hospital (Memphis) used GRSG funds to undertake a study to define and quantitate the health problems of impoverished children in an area of South Memphis. With the collaboration of a black community self-help organization, Memphis Area Project-South (MAP-South) a survey was carried out among preschool children. The findings resulted in a community nutrition program operated jointly by MAP-South and the hospital. This program is reaching over three-fourths of the infants and preschool children in this poverty area. Approximately 200 tons of food including 80,000 cans of evaporated milk (for children six months to five years of age) and 12,000 cans of Similac with Iron (for infants less than six months old) are being distributed by MAP-South each month.

7. A viral oncology group within the cancer section of Oklahoma Medical Research Foundation has isolated a virus from patients with alveolar cell carcinoma of the lung and have succeeded in growing it in tissue culture. This group has also found virus particles in biopsied lesions from a majority of patients with Bowen's disease. Homogenates of these lesions when layered over HeLa cells in tissue culture have resulted in propagation of the virus. The investigators reported that this is the first time that a virus associated with a human tumor has been grown successfully in a tissue culture.

8. Workers at the Jackson Laboratory report funds have been used to support pilot studies on animal models of human diseases produced by mutation. One of these, the shaker-2 mutated gene, produced phenylketonuria and neurological disorders. To their knowledge this is the first case of an animal that naturally excretes phenylketones, making this neurological mutant an important experimental model for the human condition of phenylketonuria.

9. In September of 1970 a rechargeable cardiac pacemaker developed at Johns Hopkins University School of Medicine was selected as one of the 100 top inventions of the year by a panel of 33 leading scientists, engineers, and research administrators as part of competition supported by Industrial Research, Inc., publishers of industrial and oceanographic magazines.

10. A summer fellowship research project at the University of Connecticut Health Center has had far-reaching effects. The medical faculty treating inner-city pediatric patients noted several children with lead poisoning back in 1967 and 1968. This suggested a pilot study might be done to determine whether these were isolated cases or whether significant numbers of children in areas of high risk might have unsuspected lead poisoning. Under the supervision of Dr. Martha Lepow, an associate professor of pediatrics Mr. Thomas Murphy, who had just completed his first year of study, conducted a project which revealed an incidence of abnormal blood lead levels in about six percent of the children from the high risk area. This study was among evidence cited by Congressman Emilio Daddario in August of 1969, when speaking for federal legislation to help detect and eliminate lead poisoning in children and it also helped to lead the Hartford City Council to adopt ordinances strengthening local control of sale and use of lead paints. A further larger-scale epidemiological study in Hartford during the summer of 1970 by a group of teenagers, supervised by Dr. Lepow and another University of Connecticut medical student, confirmed the

findings of 1969. So far, approximately 1,400 Hartford children between one and five years of age have been screened for lead poisoning. The State Department of Health has also cooperated in this work. The interest aroused by Mr. Murphy's work and others elsewhere in Connecticut led Governor Dempsey to establish a special task force on lead poisoning with Dr. Lepow and Mr. Murphy as members. This group has prepared several legislative recommendations for consideration by the 1971 session of the Connecticut legislature. Earlier this year, the Governor made the presentation of a special Upjohn Achievement Award to Mr. Murphy for his "Outstanding Application of Knowledge in Service to his Community."

11. A preliminary model of an "audiodontic device," that is a system that provides audio-communication through the teeth, has been built and tested at the University of California, Los Angeles, School of Dentistry. Development of miniaturized circuitry for an advanced model is underway.

EXAMPLES OF REPRESENTATIVE ACCOMPLISHMENTS SUPPORTED BY BSSG FUNDS

1. Washington University in St. Louis used BSSG funds to develop a five-gram radio transmitter which is small enough to be surgically implanted into the abdominal cavities of mice. The device transmits an ECG and body temperature signal a distance of 30 feet and remains active for a month or more depending on the size of the battery.

2. Funds were used by the University of Miami to initiate a program of environmental surveillance in the area west of Miami chosen for the construction of a major jetport facility.

3. Early in 1970, Dr. M. G. Rossman at Purdue University and his group succeeded in mapping the architecture of lactate dehydrogenase, an enzyme vital to metabolism. This accomplishment is regarded by the researchers as a milestone in the study of proteins.

4. A group within the Aerospace Engineering Department's High Altitude Research Laboratory at the University of Michigan has been developing a better means of detecting air pollution. Drawn through city streets in a vehicle or through smoke plumes in an aircraft, the system can give a continuous reading of different constituents at any given spot, detect the kinds of polluting constituents, and simultaneously provide a measurement of the concentration of each. Operated from an aircraft, it can give continuous readings as, for example, it moves downwind of polluting sources.

5. Dr. Robert Combs at the University of Missouri-Columbia is attempting to use the surface myopotential of non-verbal handicapped patients to allow them to communicate. The project has progressed to the point that they have coined a name "myocom" to designate Myopotential Communication. A specific example that has been successfully attempted is with a young lady that is non-verbal and has little or no control of her arms or legs. By restraining one arm she can form a partial fist. By attempting to form the fist she sets up a surface myopotential with different controllable magnitudes. The signal is processed by the "myocom" and the control of different colored lights for the expression of yes, no, or other forms of communication is accomplished by the force of the surface myopotential.

PROGRAM ANALYSIS BRANCH

1. During the past year the Director, DRR designated the Program Analysis Office as a separate Branch with responsibility for expanding the Division's data base and its analytical capabilities. A task force set up by the Director and under the guidance of the Chief, Program Analysis Branch, has been studying the Division's requirements for data reporting and program evaluation as they fit into the decision making process. For the Director's assurance that he is making excellent use of the DRR portion of the NIH dollars for better health, a vigorous analysis and evaluation of existing program activity, both failures and achievements needs to be promoted and continued. In general, the task force will seek to expand data capture of both internal and external corporate data, to accelerate data collection and retrieval, to create improved devices for simplifying, condensing, and reporting data, to develop indicators and measurements of program effectiveness based on internal/external data relationships, and to document and utilize a broad battery of analytical techniques in the process of program evaluation. The quantitative and economic techniques that have been used and will be further developed by PAB include statistical methods and statistical theory, history of science, topology, simulation, behavioral science, taxonomy, model building (mathematical and other forms), systems analysis, graph theory, economics, accounting principles, game and information theory, scientific paradigms for discovery, hypothesis and concept formation.

2. PAB devoted effort this year in support of the GRSB staff review of the GRS grantee's practices of carrying over unexpended balances from one grant period to the next. Preliminary to establishing the basis for a field study, PAB compiled a 131 page report analyzing the base of data already stored in its computer records. Besides numerous calculations and statistical representations of the variability of the data for the different classes of institutions in the program, the Report

(1) describes a general hypothesis to explain the continuing high balance of aggregate carryover,

(2) develops a mathematical model which employs statistical probability theory to predict the level of future carryover for individual institutions.

On the basis of these data PAB staff developed a modified systematic methodology for selecting an epsem sample of grantee institutions to be studied in the field. Further assistance was given to the GRSB in developing survey techniques and an interview questionnaire guide, so that necessary quantitative determinations could be made.

3. The PAB has also worked closely with the General Clinical Research Centers Branch in establishing criteria and processing appropriate data to be used in evaluating characteristics of the center's program. A joint effort was instigated to review, edit and collect research project data from page 4 of the 1970 GCRC Annual Report on the IBM 2741 Communications Terminal in PAB. The research project data included the project title, code numbers of the research area, major investigative department(s) and investigator(s) involved, source of research support, number of patient discharges and discharged patient days.

Guidelines for editing the reports and procedures for capturing the data have been written by the PAB staff. Under PAB guidance, the GCRCB prepares Page 4 of the Annual Report for data capture and assists with the keying in, verifying and editing of the data using the WYLBUR text editing and remote job entry facility supported by the Division of Computer Research and Technology. PAB coordinates the input activities, transfers the data to tape, maintains the tape files and is responsible for all facets of the project.

This system now under development will further permit automated identification of the scientific content of protocol studies conducted in the centers. PAB has produced samples of the retrieval possibilities for review by the General Clinical Research Centers Branch and OD.

4. The Program Analysis Branch collects and maintains on a regular basis a large volume of data relating to the four branches of the Division. The source documents for these data are applications, award statements, expenditures reports and annual reports. From this data bank, PAB produces publications on a regular basis such as

(1) The "Research Resource Grants" booklet which contains highlights, graphs, highlight tables, summary tables and listings pertaining to the DRR grants and reflecting the magnitude, scientific and technical diversity, geographical coverage, and general vitality of these programs of support for resources.

(2) A publication for the National Advisory Research Resources Council, "Division of Research Resources Handbook" which is a compendium of current and historical data on the appropriations and awards of the Division and its four programs, and which presents a brief description of the goals, objectives and general activities of the Division's programs.

(3) The General Research Support Program Awards Booklet which lists the name, location, type of institution, grant number and amount of award for each recipient of general

research support since the inception of the program in 1962. Summary tables by type of institution and by geographic division are also included.

(4) A Biomedical Sciences Support Program Awards Booklet which contains the same type of information for this program as described under 4.(3) for the GRS program.

(5) The General Research Support Expenditures Booklet which shows data on expenditures over a six year span for each recipient of support under this program during that period. These data are tabulated from the Annual Expenditures Reports which are filed by all institutions receiving General Research Support. Summary tables for all types of institutions and by type are also included.

(6) A Biomedical Sciences Support Program Expenditures Booklet containing the same type of information for this program as described in 4.(5) above.

The data system established by PAB for the Division contains approximately 267 data items which are defined and described in the PAB Handbooks of Definitions and Specifications for the three distinct master files maintained. A completely computerized system has been established and, depending on the nature of the task, access to the data is accomplished through the 360/20 remote or the IBM 2741 Communications Terminal. Various methods are used such as programs, the Inquiry and Reporting System referred to as Superquery, and the Publications Retrieval System similar to the Administrative Inquiry Reporting System recently introduced by the Division of Computer Research and Technology.

PAB has written, and now maintains and executes a series of computer programs and subroutines which calculate the GRS and BSS awards, punch the cards which are used to prepare the award statements by computer, and produce listings and tables which when xeroxed and reduced in size are bound and distributed as the Final GRS Awards Booklet. This publication shows for each institution the grant number, name, type, form of control, entitlement and a comparison of the newly calculated award with the amount awarded the previous year. They are presented by eligibility within type of institution and within each category arranged by size of entitlement, amount of difference between the new award and the previous year's award, percent of difference, amount of new award, and grant number. Adapting these programs and subroutines PAB produces when the need arises experimental manipulation of the GRS and BSS data in order to analyze the effect of various alterations of the formula and the resulting impact on the BSS and GRS programs. During the past year PAB developed a taxonomy of various alterations which could be done to the GRS and BSS programs and simulated by computer the effect these would have on the various grantee institutions in the programs.

Two communications projects offer prime examples of how the Division of Research Resources Information Office works closely with the media to inform various publics about the programs of the Division.

"How To Stay Alive" was an hour-long documentary which aired on the American Broadcasting Company television network May 4, 1971. The Information Office started working very closely with the producer at the idea stage for this special. In conjunction with the General Clinical Research Centers Branch, the Information Office made a number of specific suggestions which were incorporated by the producer into the show. In addition, it made the arrangements for specific program directors with special medical expertise to serve as consultants. Recognizing that a dull statistical report was not the way to demonstrate the tangible results from the Division's research resources, it made special efforts to help the producer dramatize with great accuracy a medical problem which accounts for the deaths of almost 60 percent of American men. Since clinical research centers are deeply involved in heart disease research, we were able to offer the producer a nationwide stage upon which to build a constructive report about the disease and about what research has learned on possible preventive approaches.

The Information Office did a vast amount of background research for the show in an effort to make this special as medically accurate as possible.

Four clinical research center program directors assisted greatly in sharpening the medical focus of the show. Specifically, the NIH clinical research centers received billing next to the main title of the special. Each of the Division's grantee program director experts and his institution received additional billing for participating. At the end of the special, the Division of Research Resources received full credits.

For the first time on national television, viewers had the opportunity of rating themselves on a risk profile chart. This chart, which was done to the exact specifications of a top cardiovascular specialist and clinical research center program director, included family history, diet, weight, exercise, smoking, and stress. It was carried in TV Guide and major newspapers across the country.

The Detroit News television critic called the program "what may be one of the most important specials ever shown on television."

The Chief of the Division of Cardiology, Harbor General Hospital, UCLA, wrote that it was "a very fine television program on risk factors in heart disease."

ABC said that the special gained the highest audience rating of any documentary shown on the network this year.

What made this show so successful? At least part of the answer lies in

the Information Office's great assist not only in production, but also in spreading advance word about the special. We furnished the research upon which columnist Sylvia Porter did a full piece on the cost to the Nation of heart disease and on the show. Miss Porter, whose byline appears in over 200 newspapers, noted that she "learned with pleasure that the National Institutes of Health" was participating in this special. The National Observer did a long feature story on the show and preventive aspects against heart disease, with the reporter relying on this office for extensive background and for his interviews. Pat McCormick, top UPI woman's staffer, did a feature story for the wire based on an interview with one program director, which we arranged. And there were pictures, television appearances, background stories, etc., too numerous to mention, all with Division Information Office involvement, which helped to build interest all over the Nation while it spread the message of the NIH clinical research centers quest for better health for the American people.

The Information Office helped to make all arrangements for the advance preview of the special which the American Broadcasting Company gave at the Madison Hotel in Washington. At the preview, the Director of the Division introduced the president of the television network who, in turn, introduced the film.

As for next season, there is a chance for a repeat of this fine television hour, and the possibility of a book or booklet about the show which will be available on the newstands at that time.

Turning to another Division program, the Information Office was deeply involved in a profile of each of the seven centers, together with the history of primatology and background on the development of the primate research centers program, which was incorporated into a full-length book, On the Side of the Apes, authored by Emily Hahn. Preceeded by two excerpted articles appearing in the April 17th and 24th issues of The New Yorker, the 256-page book was scheduled for release June 4 by Thomas Y. Crowell, publishers.

The Information Office has been helping Miss Hahn with her book for the past two and one-half years, furnishing background on each center's program, arranging interviews, answering questions, etc. The office even arranged for review of galleys for accuracy by primate center personnel.

In conjunction with the book, DRR information staffers have provided primate center personnel with a list of TV talk shows in their area, together with lists of magazine and science writers, and background for the placement of primate center personnel in local media.

In addition, we have helped to place Miss Hahn on the Today Show (June 9), the Arlene Francis radio show (June 3), the UPI Audio Network--a service to over 350 radio stations (taping June 2), the radio and news syndicate of the Information Center for Mature Women (June 7), Critics At Large with Harriet Van Horne (June 10), and have made numerous other radio and TV talk show contacts.

We are preparing a major article with pictures on primate research centers which will be offered by us on an exclusive basis to top newspapers in the 75-100 major markets across the U.S. sometime in late June.

We have started to work with the "JAMA Medical News" section which is planning a major round-up story on the centers for the summer or early fall.

These are but some of the activities associated with these two projects, which were admittedly major efforts, that occupied the attention of the DRR Information Office during the past year. However, this brief overview can give an indication of the sweep of the Division's information endeavors for FY 1971.

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